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Prognostic value of visceral pleural invasion in the stage $pT_{1\text{-}2}N_2M_0$ non-small cell lung cancer: A study based on the SEER registry

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ABSTRACT

Background: Visceral pleural invasion (VPI) is considered an adverse prognostic factor in non-small cell lung cancer (NSCLC). However, the prognostic roles of VPI in III/N2 NSCLC remain controversial. Therefore, this study aims to evaluate the prognostic value of VPI in patients with postoperative stage $pT_{1\text{-}2}N_2M_0$ NSCLC.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, we screened for patients with stage T1-2N2M0 NSCLC who received surgery from 2010 to 2015. To reduce baseline differences between Non-VPI group and VPI group, two-to-one propensity score matching (PSM) was performed. Cox proportional hazards regression was used to identify factors associated with survival. Overall survival (OS) was between the Non-VPI group and the VPI+ group by the Kaplan-Meier analysis.

Results: We identified 1374 postoperative NSCLC patients with stage $pT_{1\text{-}2}N_2M_0$. The majority of cases ($N = 1047$, 76.8%) are Non-VPI patients. The factors associated with VPI+ group included white race ($P < 0.0001$), and adenocarcinoma ($P < 0.0001$).

When analyzed in the total study population, VPI status remained a significant independent predictor of worse OS compared with the Non-VPI group (HR, 1.343; 95% CI, 1.083–1.665 [P=0.007]). Besides, in a subgroup analysis by VPI status, the results showed that patients without treatment exhibited a higher risk level in the Non-VPI group (P<0.0001). However, we did not find statistically significant differences among treatments in the VPI+ group (P=0.199). Mean survival time was 49.5 months (95% CI: 45.7–53.3 months) for chemotherapy alone in the Non-VPI group, compared with 41.2 months (95% CI: 35.8–46.6 months) in VPI+ groups. In both the VPI group and the non-VPI group, there is no statistical difference between adjuvant chemotherapy combined with PORT and chemotherapy alone.

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Conclusion: This study emphasizes that the presence of VPI is a poor prognostic factor, even in patients with III/N2 NSCLC. As the study shows, chemotherapy significantly improved overall survival of patients with postoperative stage $pT_{1\text{-}2}N_2M_0$ NSCLC, especially for Non-VPI patients. However, the significance of PORT is still worth further exploration.

ARTICLE INFO

Keywords: SEER; Non-small cell lung cancer; Visceral pleural invasion

Introduction

The treatment of lung cancer has made significant progress in recent years, but it is still a malignant tumor with the highest mortality and morbidity in the world.[1] American Cancer Society estimates that 228,820 new lung cancer patients and 135,720 lung cancer deaths will occur in 2020.[2]

Visceral pleural infiltration (VPI) was added to the tumor, lymph node, and metastatic (TNM) staging system by the International Union Against Cancer (UICC) to describe the characteristics of tumors in the mid-1970s.[3] One study found that lung cancer with VPI (PL1:63.6%, PL2:54.1%) had significantly lower 5-year overall survival rates than patients without VPI (PL0:75.9%).[4] Thus, VPI is considered to be an essential risk factor affecting the prognosis of patients with lung cancer.[5,6] However, there are few studies aimed to explore the effect of VPI status on the stage $T_{1\text{-}2}N_2M_0$ NSCLC.

For stage III NSCLC, it is recommended that neoadjuvant therapy combined with surgery can be used as one of the treatment options for operable patients. However, the modes of neoadjuvant treatment (simple chemotherapy, sequential radiotherapy, simultaneous radiotherapy and chemotherapy, simultaneous radiotherapy, and chemotherapy after chemotherapy) need to be further studied.[7,8] Although the 5-year overall survival rate (OS) of stage I lung cancer with completely resected was between 58% and 73%, the OS of pathological stage III lung cancer dropped sharply to less than 25%.[9] Until now, there is an urgent problem, whether radiotherapy is needed after postoperative chemotherapy for stage $T_{1\text{-}2}N_2M_0$ NSCLC is still controversial.[10]

In this study, we acquired data from the SEER database and compared the effects of different VPI status on survival of the postoperative stage $T_{1\text{-}2}N_2M_0$ NSCLC by the retrospective study.

Materials and methods

Data sources

This retrospective study based on the Surveillance, Epidemiology, and End Results (SEER) database, which includes information on cancer incidence, treatment, and survival for approximately 28% of the US population. The SEER data is freely available for cancer-based epidemiology investigation and survival analysis. We used the SEER*Stat software Version 8.3.6 to extract research data.

Study population

From the SEER database, patients aged $\geq$ 20 years who were histologically diagnosed with NSCLC from January 2010 to December 2015 were included for the cohort. We used codes 00,

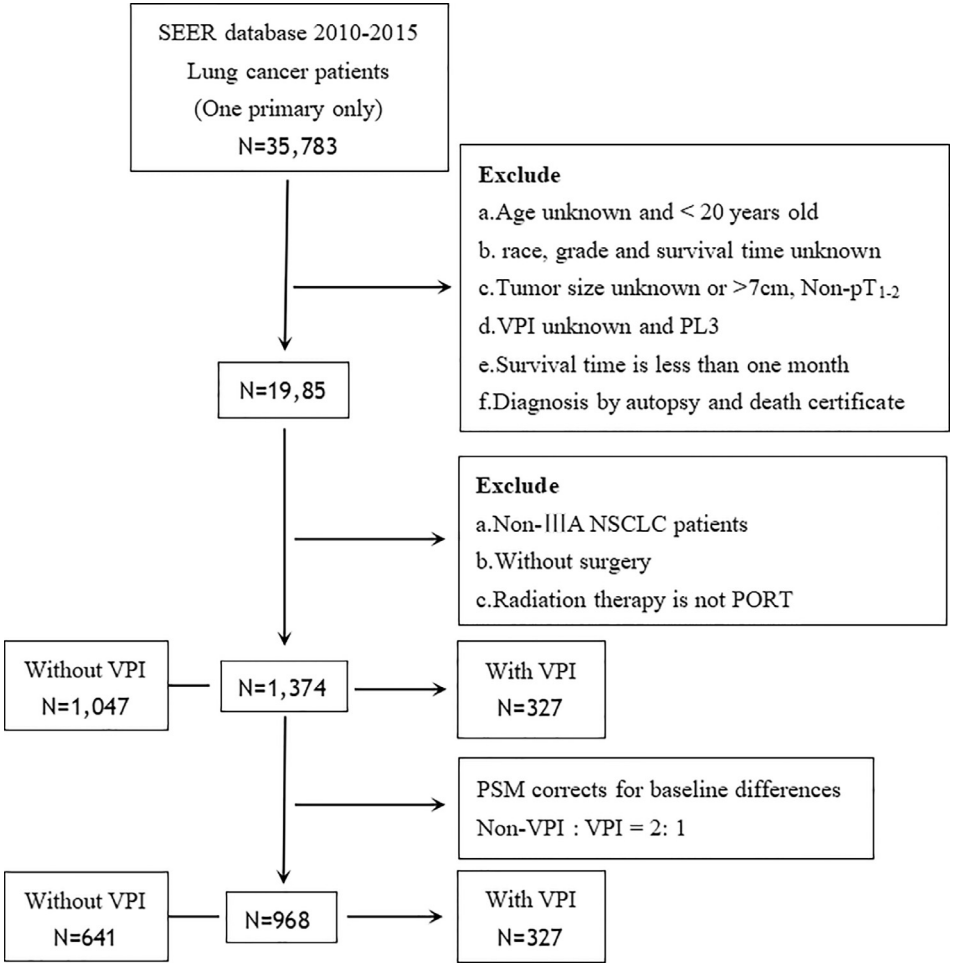

Fig. 1. Flow chart of patient selection.

10, 20 in cs site-specific factor 2 to get VPI status PL0, PL1, and PL2. PL1 and PL2 indicated the presence of VPI, while PL0 represents the absence of VPI. We reclassified Histologic grade as low grade (well-differentiated and moderately differentiated) or high grade (poorly differentiated and undifferentiated). The study included patients for whom NSCLC was their first and only primary malignancy, with the tumor T1-2, lymph node (LN) involvement (N2), and VPI status (PL0-PL2). VPI status has been brought into the SEER database since 2010. Therefore, all the patients included were diagnosed between 2010 and 2015. The selection process was as follows (Fig. 1): we excluded patients with unknown age, race, grade and survival time. We further excluded patients with age <20 years old, and survival time < 1 month, as well as cases with unknown tumor size and not pathological T1-2. We also excluded patients with unknown VPI status and PL3. Furthermore, we excluded patients with small cell lung cancer, incomplete dates for follow-up and diagnosis by autopsy and death certificate. The last, we excluded patients without IIIA NSCLC and surgery. Of the patients treated with radiotherapy, we only selected those who received PORT.

We extracted the following data for each case: patient ID, age at the time of diagnosis, gender, race, neoplastic grade, Histology, VPI status, AJCC staging information, therapeutic method, survival months, and vital status.

Table 1
Baseline characteristics of all patients.

Characteristic	Before PSM (*N*=1374)			After PSM (*N*=968)		
	Non-VPI *N*=1047 (76.8)	VPI *N*=327 (23.2)	*P*-value	Non-VPI *N*=641 (66.2)	VPI *N*=327 (33.8)	*P*-value
Gender			0.338			0.891
Male	512 (48.9)	150 (45.9)		297 (46.3)	150 (45.9)	
Female	535 (51.1)	177 (54.1)		344 (53.7)	177 (54.1)	
Age (year)			0.070			0.291
20-59	298 (28.5)	82 (25.1)		182 (28.4)	82 (25.1)	
60-74	518 (49.5)	153 (46.8)		306 (47.7)	153 (46.8)	
75+	231 (22.1)	92 (28.1)		153 (23.9)	92 (28.1)	
Race			<0.0001*			0.720
White	851 (81.3)	269 (82.3)		538 (83.9)	269 (82.3)	
Black	117 (11.2)	16 (4.9)		32 (5.0)	16 (4.9)	
Other†	79 (7.5)	42 (12.8)		71 (11.1)	42 (12.8)	
Grade			0.266			0.531
Low Grade (Grade I-Grade II)	562 (53.7)	187 (57.2)		353 (55.1)	187 (57.2)	
High Grade (Grade III- Grade IV)	485 (46.3)	140 (42.8)		288 (44.9)	140 (42.8)	
Histology			<0.0001*			0.987
Adenocarcinoma	677 (64.7)	254 (77.7)		495 (77.2)	254 (77.7)	
SCC♦	242 (23.1)	42 (12.8)		84 (13.1)	42 (12.8)	
0ther NSCLC*,*	128 (12.2)	31 (9.5)		62 (9.7)	31 (9.5)	
Treatment			0.346			0.150
Chemotherapy + PORT	384 (36.7)	117 (35.8)		244 (38.1)	117 (35.8)	
Chemotherapy	369 (35.2)	115 (35.2)		219 (34.2)	115 (35.2)	
PORT	42 (4)	7 (2.1)		30 (4.7)	7 (2.1)	
Untreated	252 (24.1)	88 (26.9)		148 (23.1)	88 (26.9)	

Other† includes American Indian, Alaska Native, Asian/Pacific Islander, and unspecified.
SCC♦:Squamous cell carcinoma; NSCLC*,*:Non-small cell lung cancer.
VPI:Visceral pleural invasion, including PL1 and PL2.
PL1:Tumor that invades beyond the elastic layer.
PL2:Tumor that extends to the surface of the visceral pleura (AJCC Staging Manual 7th Edition).

Statistical analysis

The clinicopathological characteristics between the four groups were evaluated using the Pearson X^2 test. To reduce baseline differences between Non-VPI group and VPI group, two-to-one propensity score matching (PSM) was performed. Cox proportional hazards multivariable regression was performed to assess the impact of different therapeutic methods on overall mortality for demographic factors, tumor grade, histology type, and VPI status. We used Kaplan-Meier analysis with the log-rank test to the estimated OS.

Furthermore, we performed subgroup analyses, stratified by VPI status, to examine the effect of adjuvant treatment on overall survival for patients with different VPI status of the disease. All statistical analyses were made using IBM SPSS 24, and all survival curves were constructed using GraphPad 7.0. All *P* values were two-sided, and $P < 0.05$ were considered significant.

Results

Patient characteristics

We identified 1374 cases that match the filter criteria. After the PSM, there were still 968 cases in our study population. The cohort selection process is shown in Fig. 1, and the characteristics of these patients are shown in Table 1. In total, 53.8% were female, and 46.2% were male.

Table 2
Univariate and multivariate analysis of clinicopathological factors affecting outcome.

Clinical parameters	Univariate	Multivariate		
	P-value	HR	95% CI	*P*-value
Gender	<0.0001			<0.0001
Male		Reference		
Female		0.621	0.503–0.767	
Age (years)	<0.0001			<0.0001
20-59		Reference		
60-74		1.339	1.017–1.763	0.038
75+		2.131	1.567–2.897	<0.0001
Race	0.407	NA		
White				
Black				
Other†				
Grade	0.297	NA		
Low Grade				
High Grade				
Histology	0.593			0.313
Adenocarcinoma		Reference		
SCC♦		1.055	0.776–1.434	0.735
0ther NSCLC*,*		0.769	0.537–1.102	0.152
VPI status	0.006			0.007
Non-VPI		Reference		
VPI		1.343	1.083–1.665	
Therapy	<0.0001			0.011
Untreated		Reference		
Chemotherapy + PORT		0.722	0.550–0.946	0.018
Chemotherapy		0.631	0.478–0.833	0.001
PORT		0.703	0.402–1.230	0.217
		0.874	0.674–1.134	0.312*

Other† includes American Indian, Alaska Native, Asian/Pacific Islander, and unspecified
SCC♦:Squamous cell carcinoma; NSCLC*,*:Non-small cell lung cancer
VPI:Visceral pleural invasion, including PL1 and PL2
PL1:Tumor that invades beyond the elastic layer
PL2:Tumor that extends to the surface of the visceral pleura (AJCC Staging Manual 7th Edition)
P*: Chemotherapy VS Chemotherapy + PORT

The majority of patients were whites, followed by blacks and others (83.4%, 5%, 11.6%, respectively; *P*=0.720). The most common histology of patients was Adenocarcinoma (77.4%), followed by SCC (13%) and other NSCLC (9.6%, *P*= 0.987).

Of the total 968 patients, 327 cases were diagnosed with VPI+, while Non-VPI was identified in 641 patients. Among all patients, 361(37.3%) underwent chemotherapy and PORT, 334(34.5%) received single chemotherapy, 37(3.8%) received PORT, and 236(24.4%) received no adjuvant treatment. There was no significant difference in the VPI status among different treatments (*P*= 0.150). The baselines of Non-VPI group and VPI group are balanced. Detailed clinical characteristics were summarized in Table 1.

Survival analysis

The results of the multivariate Cox analysis of factors affecting outcomes among all patients are listed in Table 2. Factors associated with improved OS included younger age, female sex, non-VPI, and receiving treatment.

Generally speaking, there was a statistical difference in OS between the VPI group and the non-VPI group. Compared with the non-VPI group, VPI+ remained a significant independent predictor of worse OS (HR, 1.343; 95% CI, 1.083–1.665 [*P*=0.007]). The median OS of the non-VPI group and VPI group was 52 (95% CI: 43.5–60.5 months) and 39 months (95% CI: 33.8–44.2

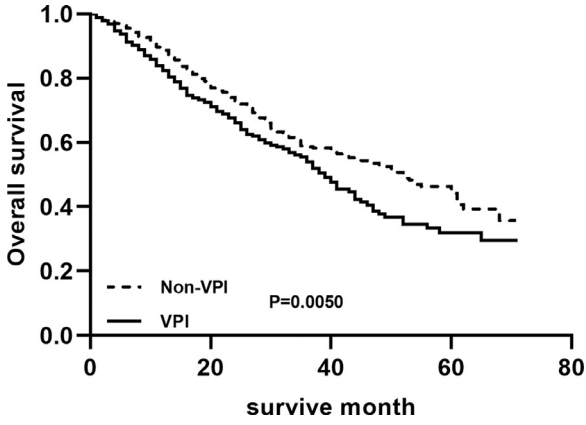

Fig. 2. Overall survival curve of patients with VPI and Non-VPI.

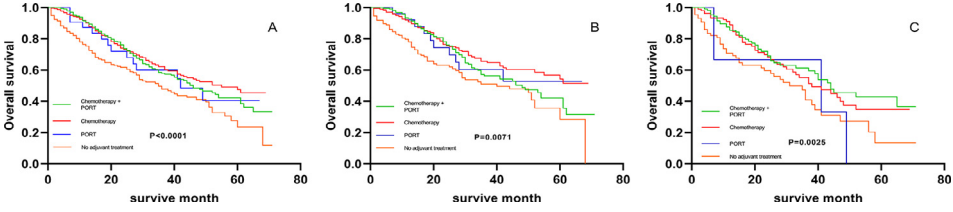

Fig. 3. Overall survival curve of chemotherapy and PORT, chemotherapy, PORT, and no adjuvant treatment in different cohorts. (A) Comparison of overall survival rate among chemotherapy and PORT, chemotherapy, PORT, and no adjuvant therapy in patients with stage T1-2N2M0 NSCLC; (B) comparison of overall survival rate among chemotherapy and PORT, chemotherapy, PORT, and no adjuvant therapy in patients with stage T1-2N2M0 NSCLC without VPI; (C)comparison of overall survival rate among chemotherapy and PORT, chemotherapy, PORT, and no adjuvant therapy in patients with stage T1-2N2M0 NSCLC with VPI.

months), respectively. Furthermore, the 5-year OS rate was 44% for the non-VPI group, and 32% for the VPI group (P=0.0050) (Fig. 2). Besides, the mean OS time of chemotherapy in non-VPI and VPI groups was 49.5 months (95% CI: 45.7–53.3 months) and 41.2 months (95% CI: 35.8–46.6 months), respectively.

In the VPI group, the treatment is not a factor affecting the prognosis (P=0.199). However, there was a significant difference only between the chemotherapy group and the untreated group (P=0.041). In addition, there was no statistical difference between chemotherapy combine with PORT and chemotherapy groups. The specific values of variables were shown in Table 3

Unadjusted survival curves were used to describe survival differences among four treatment groups in different cohorts (Fig. 3). There was a statistical difference in OS between the Non-VPI group and VPI group (P =0.007). Specifically, the 5-year OS rate was 42.2%, 47.5%, 40.4%, and 23.7% for patients who underwent chemotherapy and PORT, chemotherapy, PORT, and no adjuvant treatment ($p<0.0001$) (Fig. 3(A)).

In secondary analyses stratified by VPI status. In the non-VPI group, there was a statistical difference in gender, age, and treatments (Table 3). The mean OS time of chemotherapy and PORT, chemotherapy,PORT, and no adjuvant treatment was 45.5 (95% CI: 41.8–49.2 months), 49.5 (95% CI: 45.7–53.3 months), 46.1 (95% CI: 36.3–55.9 months) and 38.4 months (95% CI: 33.6–43.2 months), respectively. The 5-year OS rate was 42% for chemotherapy combine radiotherapy, 54% for single chemotherapy, 53% for single radiotherapy, and 29% for the untreated group (P= 0.0071) (Fig. 3(B)).

Table 3
Multivariate analysis of clinicopathological factors affecting outcomes in Non-VPI and VPI.

Clinical parameters	Non-VPI (*N*=641)		VPI (*N*=327)	
	HR (95% CI)	P-value	HR(95% CI)	*P*-value
Gender		<0.002		0.001
Male	Reference		Reference	
Female	0.660 (0.505–0.863)		0.548 (0.386–0.779)	
Age (years)		<0.0001		0.044
20–59	Reference		Reference	
60–74	1.557 (1.096–2.212)	0.014	1.076 (0.685–1.689)	0.751
75+	2.333 (1.582–3.441)	<0.0001	1.794 (1.061–3.034)	0.029
Race		NA		NA
White				
Black				
Other†				
Grade		NA		NA
Low Grade				
High Grade				
Unknown				
Histology		0.213		0.513
Adenocarcinoma	Reference		Reference	
SCC♦	1.248 (0.857–1.818)	0.249	0.816 (0.472–1.410)	0.466
0ther NSCLC*,*	0.753 (0.467–1.214)	0.244	0.758 (0.434–1.326)	0.332
Therapy		0.020		0.199
Untreated	Reference		Reference	
Chemotherapy +PORT	0.767 (0.550–1.071)	0.120	0.673 (0.425–1.065)	0.091
Chemotherapy	0.574 (0.402–0.821)	0.002	0.604 (0.372–0.980)	0.041
PORT	0.609 (0.313–1.187)	0.145	1.064 (0.374–3.030)	0.907
	0.749 (0.409–1.045)	0.089*	0.897 (0.588–1.370)	0.616*

Other† includes American Indian, Alaska Native, Asian/Pacific Islander, and unspecified
SCC♦:Squamous cell carcinoma; NSCLC*,*:Non-small cell lung cancer
VPI:Visceral pleural invasion, including PL1 and PL2
PL1:Tumor that invades beyond the elastic layer.
PL2:Tumor that extends to the surface of the visceral pleura (AJCC Staging Manual 7th Edition).
*P**: Chemotherapy VS Chemotherapy + PORT.

In the VPI group, there was a statistical difference in gender and age. However, when it comes to treatment groups, there is no statistical difference in OS (Table 3). The median OS of chemotherapy and PORT, chemotherapy, PORT, and no adjuvant treatment was 44 (95% CI: 33.3–54.7 months), 38 (95% CI: 26.2–49.8 months), 41 months (95% CI: 0–91.9 months) and 31 months (95% CI: 22.8–39.2 months), respectively. The 5-year OS rate was 43% for chemotherapy and PORT, 35% for chemotherapy, 0% for PORT, and 14% for the untreated group (*P*=0.0025) (Fig. 3(C)).

Discussion

Nowdays, the treatment of patients with stage III/N2 NSCLC is still controversial due to the highly heterogeneous of the disease. Although comprehensive treatment is valid, the effects of surgery, chemotherapy, and radiotherapy have not been fully defined, and the optimal treatment method has not been determined.[11] There is an urgent need for personalized risk stratification and treatment. Therefore, it is critical to identify and verify the high risk of patients suitable for adjuvant therapy.

Recent studies have pointed out that VPI is a poor prognostic factor.[3,5,12,13] One study[5] suggested that VPI conferred a significantly worse survival in N0, not in N1 or N2 disease. In addition, Hiroyuki Adachi et al.[12] have reported the impact of VPI on postoperative survival in patients with NSCLC who have N0 or N1 metastasis. They found that patients with VPI have worse survival, and there was no difference in survival according to the presence or absence

of VPI in patients with N2 disease. Fujimoto[14] also reported that VPI was a predictor of poor survival in patients with completely resected N1 NSCLC. However, it is not clear whether the status of VPI has an impact on stage $T_{1\text{-}2}N_2M_0$ NSCLC. In our study, we found that VPI is still a risk factor for prognosis in patients with stage $T_{1\text{-}2}N_2M_0$ NSCLC. The median OS of the non-VPI group and VPI group was 52 (95% CI: 43.5–60.5 months) and 39 months (95% CI: 33.8–44.2 months). Our results are different from the above studies,[5] which may be due to the fact that chemotherapy is not taken into account in the above research. The reason for the different results between this and Hiroyuki Adachi et al.[12] may be that the databases studied are different. For resected IIIA NSCLC patients, adjuvant chemotherapy is considered the gold standard after surgery.[15] In our study, postoperative adjuvant chemotherapy can effectively improve patient survival. This result is also consistent with current treatment strategies. Besides, we found that among patients receiving chemotherapy, the median survival time of patients in the non-VPI group was 15 months longer than that in the VPI+ group. Therefore, we strongly recommend that resected IIIA NSCLC patients with Non-VPI should receive adjuvant chemotherapy. Although this result was obtained using the SEER database, we believe that our results include valuable new information that will facilitate advanced confirmatory research programs, as the previous series of studies have rarely covered the impact of VPI on patients with stage $pT_{1\text{-}2}N_2M_0$ NSCLC.

As far as we know, the relative benefits of radiotherapy in the platinum-based standard chemotherapy environment for IIIA (N2) NSCLC have not been documented. Several retrospective studies have reported favorable outcomes for postoperative radiotherapy in stage III-N2 NSCLC.[16,17] However, according to the results of a meta-study,[18] the risk of local recurrence of PORT is significantly lower, but this effect cannot be translated into significant OS benefits. Our study shows that there is no statistical difference between adjuvant chemotherapy combined with PORT and chemotherapy alone, and there is no additional survival benefit from survival analysis. Our study has limitations because the SEER database does not provide detailed information about radiotherapy, so the results need to be further verified in clinical practice. Therefore, the significance of radiotherapy in postoperative stage $pT_{1\text{-}2}N_2M_0$ NSCLC patients is still worth further exploration.

The study had some limitations. First, this was a retrospective study rather than a prospective randomized study, so inherent selection bias was inevitable. Second, performance status (PS) is an important prognostic factor in NSCLC. Third, for NSCLC patients with gene mutations, such as EGFR or ALK mutations, targeted therapy has become a first-line treatment. However, these specific information is not available in the SEER database. Finally, our study is base on the SEER database, so the conclusions might only apply to patients in the United States.

In conclusion, this is the first large-scale database study to examine the prognostic value of VPI in patients with postoperative stage $pT_{1\text{-}2}N_2M_0$ NSCLC. This study shows that VPI is a poor prognostic factor in patients with III/N2 NSCLC. And chemotherapy significantly improved overall survival of NSCLC patients with postoperative stage $pT_{1\text{-}2}N_2M_0$, especially for Non-VPI patients. However, the significance of PORT is still worth further exploration.

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