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Prognostic value of adjuvant therapy in T4 non-small cell lung cancer: An inverse probability of treatment weighting analysis

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Keywords
Adjuvant chemotherapy; inverse probability of treatment weighting; non-small cell lung cancer; Surveillance, Epidemiology, and End Results (SEER) registry; survival.

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Abstract

Background: According to the current clinical guidelines, chemoradiotherapy is considered the standard treatment for locally advanced non-small cell lung cancer (NSCLC). We analyzed the prognostic effect of adjuvant chemotherapy (ACT) in resected patients using the new eighth tumor node metastasis (TNM) staging systems based on the Surveillance, Epidemiology and End Results database.

Methods: We identified 3008 patients with stage IIIA NSCLC (T4N0M0) who underwent sublobar resection, lobectomy, or pneumonectomy. Covariates affecting treatment selection or survival were included as part of propensity score models for matching and weighting. The effect of ACT on survival was assessed, stratified by postoperative radiation therapy (PORT) use, tumor size, and age.

Results: Analyses of 2016 patients were conducted with standardized differences in covariates < 10% after matching. ACT was associated with significantly improved five-year overall survival (51.1% vs. 39.7%; $P = 0.0260$) in patients aged 21–65 with > 7 cm tumors, even after adjusting for the presence or absence of the superior sulcus ($P = 0.0003$). No significant outcomes were observed using other stratifications in the matched analysis. Moreover, ACT with PORT conferred a potential survival benefit in 21–65-year-old patients with 0–7 cm tumors (for all causes of death: hazard ratio 0.414, 95% confidence interval 0.251–0.684).

Conclusion: In this population-based cohort, ACT prolonged the survival of patients aged 21–65 with a tumor > 7 cm, with or without PORT. Inverse probability of treatment weighting can estimate the treatment effect and is suitable for use with survival data.

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide, with the vast majority of patients having locally advanced or metastatic disease (stage IIIA/IIIB or IV) at the time of diagnosis; this condition remains a challenge to management of the disease.[1] For

technically resectable patients with stage IIIA NSCLC, surgical methods are recommended, despite high recurrence and mortality rates after surgery.[2,3] The use of adjuvant chemotherapy (ACT) with or without radiotherapy for stage IIIA tumors has been validated in several clinical trials[4,5] and is recommended in the current National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines).[6] However, stage IIIA–N0 patients with certain characteristics cannot definitively benefit from ACT and this point requires investigation with a large sample.

In the eighth edition American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) staging system, T3 tumors > 7 cm in the greatest dimension or that invade the mediastinum were upgraded to T4; N0M0 cases among them were thus restaged from IIB to IIIA, and as a result, T4 tumors became more heterogeneous.[7] However, the prognostic value of ACT in differing tumor size and age groups is controversial.[8–12] Furthermore, radiation is used in most cases concomitantly with chemotherapy, which may confound assessment of the efficacy of chemotherapy. Therefore, a more detailed evaluation of the prognostic value of ACT is needed. Our study aimed to clarify the relationship between the prognostic value of ACT and tumor size and age in resected patients with stage IIIA–N0 (T4N0M0) NSCLC. Our secondary aim was to discuss the prognostic effect of ACT on patients without and with postoperative radiation therapy (PORT).

Methods

Data selection

The Surveillance, Epidemiology, and End Results (SEER) database collects cancer data from population-based registries covering approximately 30% of the United States population.[1] We used Incidence-SEER 18 Regs Custom Data submitted in November 2017 via SEER*Stat version 8.3.5 (https://seer.cancer.gov/data/). This study was reviewed by our institutional review board and classified as exempt. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The criteria for data selection were as follows: patients aged > 20, diagnosed between 2004 and 2015, whose NSCLC was the first or only primary tumor (Figure S1). Patients diagnosed at autopsy or on their death certificate, who died within four months, or with an inexact age or tumor size were excluded.[13] We identified patients who were reclassified as T4N0M0 based on the eighth TNM staging system.[7] Calculation was manually implemented according to the CS-Tumor Size, CS-Extension, CS Mets at DX, CS Site-Specific Factor 1, Size Extension Mets SSF1 AJCC 6 tables, and Size Extension SSF1 AJCC 7 T tables from CS Coding Instruction version 02.05.[14] Some 0–7 cm tumors classified as T3 according to the seventh edition may upgrade to T4 if they involve the mediastinum; these tumors were excluded from this study because the anatomic structures of the CS-Extension code were at a value of 600, and this one code was unable to accurately distinguish these cases from T3 tumors.[15] Patients with < 1 lobe resected or who underwent lobectomy or pneumonectomy were included. Cases not administered radiation, who received radiotherapy prior to surgery, or in which a sequence was unknown were excluded.

Five-year overall survival (OS) and lung cancer-specific survival (LCSS) outcomes were determined using variables from the SEER records. Deaths from any cause based on the Vital Status Recode item, deaths attributed to NSCLC based on the Cause of Death to Site Recode item in conjunction with the ICD codes, or other causes of death were considered censoring events. Survival time was censored at the time of loss to follow-up or the date of death from other causes.[16]

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The baseline characteristics of each group were compared using Wilcoxon's rank sum test for age and tumor size and the chi-square test for other variables. Before analysis, we found that survival was different between patients diagnosed before and after 2010; therefore, we set a binary variable for year of diagnosis. To reduce the differences in baseline variables between groups, we used the propensity score matching (PSM) method. The exposure for the propensity score (PS) model was the presence of ACT. PSs were calculated using a logistic regression model. The PS model included covariates that were marginally associated with survival in univariate or multivariable analyses ($P < 0.20$),[17] as well as covariates that contributed to whether patients received ACT. Patients were matched on the basis of PS via the greedy nearest-neighbor method, with a matching ratio of 1:1. The logit-PS was multiplied by 0.2 as a caliper for matching.[18] Standardized mean difference (SMD) was adopted to evaluate the balance between covariates. An absolute value of SMD < 10% is acceptable. After matching, survival curves were estimated using the Kaplan–Meier method, and a paired z-test was used to compare survival curves between groups.[18,19]

In addition to matched analysis, the treatment effect was estimated using the inverse probability of treatment weighting (IPTW) using a Cox model that included receipt of ACT as a variable. This method uses weights to construct virtual samples, in which the distribution of

Table 1 Baseline characteristics of T4N0M0 non-small cell lung cancer patients before and after propensity score matching

	Before matching			After matching			
Characteristic	No ACT (*n* = 1696)	ACT (*n* = 1312)	*P*	No ACT (*n* = 1008)	ACT (*n* = 1008)	*P*	SMD†(%)
Age, years							
Median	70	65	< 0.0001	66	66	0.6013	−2.33
Range	25–94	28–88		25–91	28–88		
Tumor size, cm							
Median	7.1	7.5	< 0.0001	7.5	7.5	0.6976	2.60
Range	0.2–18.4	0.4–23.0		0.5–19.0	0.4–22.8		
Gender, N (%)							
Male	957 (56.43%)	752 (57.32%)	0.6250	580 (57.54%)	586 (58.13%)	0.7867	1.19
Female	739 (43.57%)	560 (42.68%)		428 (42.46%)	422 (41.87%)		
Race, N (%)							
White	1439 (84.85%)	1083 (82.55%)	0.0376	836 (82.94%)	833 (82.64%)	0.9279	−0.79
Black	149 (8.79%)	152 (11.58%)		109 (10.81%)	114 (11.31%)		1.59
Other	108 (6.36%)	77 (5.87%)		63 (6.25%)	61 (6.05%)		−0.83
Marital status, N (%)							
Married	964 (56.84%)	803 (61.20%)	0.0159	616 (61.11%)	596 (59.13%)	0.3631	−4.04
Unmarried	732 (43.16%)	509 (38.80%)		392 (38.89%)	412 (40.87%)		
Insurance, N (%)							
Insured	1115 (65.74%)	961 (73.25%)	< 0.0001	723 (71.73%)	726 (72.02%)	0.8819	0.65
Uninsured/unknown	581 (34.26%)	351 (26.75%)		285 (28.27%)	282 (27.98%)		
County attributes in education, N (%)							
First quantile‡	428 (25.24%)	347 (26.45%)	0.5011	257(25.50%)	263 (26.10%)	0.5906	
Second quantile	434 (25.59%)	320 (24.39%)		243(24.11%)	260 (25.79%)		
Third quantile	410 (24.17%)	335 (25.53%)		248(24.60%)	250 (24.80%)		
Fourth quantile	424 (25.00%)	310 (23.63%)		260(25.79%)	235 (23.31%)		
County attributes in median family income, N (%)							
First quantile‡	433 (25.53%)	362 (27.59%)	0.0235	242 (24.11%)	265 (26.29%)	0.4340	5.02
Second quantile	438 (25.83%)	340 (25.91%)		263 (26.09%)	253 (25.10%)		−2.27
Third quantile	384 (22.64%)	292 (22.26%)		226 (22.42%)	217 (21.53%)		−2.15
Fourth quantile	441 (26.00%)	318 (24.24%)		277 (27.48%)	273 (27.08%)		−0.89
Location, n (%)							
Upper lobe	879 (51.83%)	699 (53.28%)	0.7843	501 (49.70%)	515 (51.09%)	0.9042	2.78
Middle lobe	68 (4.01%)	48 (3.66%)		36 (3.57%)	38 (3.77%)		1.06
Lower lobe	588 (34.67%)	436 (33.23%)		369 (36.61%)	359 (35.62%)		−2.06
Main bronchus, Other	161 (9.49%)	129 (9.83%)		102 (10.12%)	96 (9.52%)		−2.02
Laterality, N (%)							
Left	676 (39.86%)	532 (40.55%)	0.7018	396 (39.29%)	405 (40.18%)	0.6822	
Right	1020 (60.14%)	780 (59.45%)		612 (60.71%)	603 (59.82%)		
Histology, N (%)							
Adenocarcinoma	736 (43.40%)	634 (48.32%)	0.0016	478 (47.41%)	473 (46.92%)	0.9667	−0.98
Bronchioalveolar carcinoma	207 (12.20%)	104 (7.93%)		89 (8.83%)	97 (9.62%)		2.73
Large cell carcinoma	67 (3.95%)	56 (4.27%)		43 (4.27%)	39 (3.87%)		−2.02
Squamous cell	552 (32.55%)	415 (31.63%)		317 (31.45%)	318 (31.55%)		0.22
Adenocarcinoma with mixed subtype	134 (7.90%)	103 (7.85%)		81 (8.04%)	81 (8.04%)		0.00
Differentiation, N (%)							
Well	258 (15.21%)	160 (12.20%)	0.0044	139 (13.79%)	139 (13.79%)	0.9926	0.00
Moderately	614 (36.20%)	446 (33.99%)		359 (35.62%)	354 (35.12%)		−1.05
Poorly	614 (36.20%)	561 (42.76%)		399 (39.58%)	397 (39.38%)		−0.41
Undifferentiated	59 (3.48%)	40 (3.05%)		33 (3.27%)	35 (3.47%)		1.11
Unknown	151 (8.91%)	105 (8.00%)		78 (7.74%)	83 (8.24%)		1.84

Table 1 Continued

Characteristic	Before matching			After matching			
	No ACT (n = 1696)	ACT (n = 1312)	P	No ACT (n = 1008)	ACT (n = 1008)	P	SMD†(%)
Number of lymph nodes examined, N (%)							
0	152 (8.96%)	150 (11.43%)	0.0602	100 (9.92%)	102 (10.12%)	0.8884	0.67
1–10	861 (50.77%)	603 (45.96%)		471 (46.73%)	470 (46.63%)		−0.20
11–20	380 (22.41%)	310 (23.63%)		244 (24.21%)	239 (23.70%)		−1.19
> 20	148 (8.73%)	124 (9.45%)		92 (9.13%)	104 (10.32%)		4.02
Unknown§	155 (9.13%)	125 (9.53%)		101 (10.01%)	93 (9.23%)		−2.65
Year of diagnosis, N (%)							
2004–2009	1090 (64.27%)	671 (51.14%)	< 0.0001	551 (54.66%)	558 (55.36%)	0.7540	1.41
2010–2015	606 (35.73%)	641 (48.86%)		457 (45.34%)	450 (44.64%)		
Surgery type, N (%)							
Sublobar resection	255 (15.04%)	209 (15.93%)	0.0632	152 (15.08%)	147 (14.58%)	0.8878	−1.41
Lobectomy	1273 (75.05%)	941 (71.72%)		742 (73.61%)	741 (73.51%)		−0.23
Pneumonectomy	168 (9.91%)	162 (12.35%)		114 (11.31%)	120 (11.91%)		1.87
PORT use, N (%)							
Without	1572 (92.69%)	981 (74.77%)	< 0.0001	884 (87.70%)	882 (87.50%)	0.8925	−0.61
With	124 (7.31%)	331 (25.23%)		124 (12.30%)	126 (12.50%)		

†Standardized mean difference (SMD) is only calculated and shown for the variables included in the propensity score model. ‡First quantile denotes the most county attributes. §Lymph nodes were examined but the exact number is unknown. ACT, adjuvant chemotherapy; PORT, postoperative radiation therapy.

covariables is independent of the processing allocation.[20] To avoid extreme weights that may result in unreliable outcomes, we used stabilized weights, defined as sw = pt/ps for the treated group and sw = (1 − pt)/(1 − ps) for the control group (pt denotes the proportion receiving ACT in the sample).[21] Two-tailed P values < 0.05 were considered statistically significant.

Results

A total of 3008 patients were identified from the SEER database, of which 1312 received ACT. The baseline clinical characteristics, grouped according to the presence or absence of ACT, are shown in Table 1. Compared to patients who did not receive ACT, we observed that patients who received ACT were more likely to be younger (P < 0.0001), married (P = 0.0159), and insured (P < 0.0001), and were less likely to be white (P = 0.0376). Patients with smaller diameter tumors (P < 0.0001), who lived in a county with a higher median family income (P = 0.0235),[22] and with histology other than adenocarcinoma (P = 0.0016) and poorly differentiated (P = 0.0044) were less likely to receive ACT. The use of ACT was higher among patients who were diagnosed during or after 2010 (P < 0.0001); patients who received ACT were also more likely to receive PORT (P < 0.0001).

The complete results of univariate and multivariate analyses of OS are shown in Table 2. Factors including the use of ACT, being female, being of a race other than white or black, living in a county with a higher median family income, lymph node examination, and diagnosis during or after 2010 led to a reduced hazard to the reference. Conversely, the use of PORT, increased age, larger tumor size, being unmarried, having a tumor that originated in the lower lobe or main bronchus or that was poorly differentiated, or the presence of squamous cell carcinoma or adenocarcinoma of mixed type all had a negative impact on survival (Table 2). After PSM, 1008 matched pairs of patients grouped by ACT use were generated. The SMDs are shown in Table 1, and those calculated from virtual samples generated by IPTW based on PS are displayed in Table S1. Absolute values for the SMDs of covariates in the PS model were all < 10%, indicating that the covariates between groups were well balanced. To clearly describe the relationship between tumor size and age and the prognostic value of ACT, we stratified patients into four classes to perform survival comparison: tumors 0–7 cm, age 21–65; tumors 0–7 cm, age > 65; tumors > 7 cm, age 21–65; and tumors > 7 cm, age > 65. Survival curves based on matched analysis are shown in Figures 1 and S2–S5.

We observed that survival significantly differed only between patients aged 21–65 with tumors > 7 cm treated without and with ACT; in the entire cohort, the five-year OS was 39.7% versus 51.1% (P = 0.0260) and the five-year LCSS was 47.8% versus 61.1% (P = 0.0579), respectively (Fig 1). This outcome was not observed in other classes (Figures S2–S4). In patients who did not receive PORT in

Table 2 Results of univariate and multivariable analyses of overall survival before propensity score matching

	Univariate			Multivariable		
Characteristic	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.021	1.016–1.026	< 0.0001	1.024	1.018–1.029	< 0.0001
Tumor size	1.038	1.027–1.050	< 0.0001	1.044	1.032–1.056	< 0.0001
Gender			< 0.0001			< 0.0001
Male	Reference			Reference		
Female	0.731	0.662–0.807	< 0.0001	0.751	0.676–0.834	< 0.0001
Race			0.0112			0.0019
White	Reference			Reference		
Black	1.070	0.912–1.256	0.4076	1.174	0.994–1.386	0.0596
Other	0.730	0.585–0.909	0.0050	0.723	0.578–0.903	0.0043
Marital status			0.0781			0.0277
Married	Reference			Reference		
Unmarried	1.091	0.990–1.203	0.0781	1.121	1.013–1.241	0.0277
Insurance			0.0598			0.0716
Insured	Reference					
Uninsured/unknown	1.102	0.996–1.219	0.0598			
County attributes in education			0.7918			
First quantile†	0.938	0.770–1.144	0.5273			
Second quantile	0.949	0.794–1.135	0.5690			
Third quantile	1.022	0.860–1.213	0.8080			
Fourth quantile	Reference					
County attributes in median family income			0.2944			0.1302
First quantile†	0.866	0.730–1.027	0.1023	0.845	0.693–1.030	0.0961
Second quantile	0.925	0.783–1.094	0.3626	0.841	0.698–1.014	0.0696
Third quantile	0.866	0.730–1.027	0.0978	0.823	0.692–0.977	0.0265
Fourth quantile	Reference			Reference		
Location			0.0007			0.0284
Upper lobe	Reference			Reference		
Middle lobe	1.263	0.985–1.620	0.0658	1.329	1.031–1.713	
Lower lobe	1.222	1.100–1.357	0.0002	1.260	1.129–1.406	<0.0001
Main bronchus, Other	1.211	1.019–1.440	0.0302	1.254	1.048–1.501	0.0135
Laterality			0.2385			
Left	Reference					
Right	0.943	0.855–1.040	0.2385			
Histology			<0.0001			<0.0001
Adenocarcinoma	Reference			Reference		
Bronchioalveolar carcinoma	0.862	0.729–1.019	0.0814	0.844	0.706–1.010	0.0640
Large cell carcinoma	1.250	0.982–1.592	0.0697	1.107	0.826–1.485	0.2965
Squamous cell	1.234	1.105–1.378	0.0002	1.206	1.060–1.446	0.0027
Adenocarcinoma with mixed subtype	1.328	1.116–1.581	0.0014	1.323	1.111–1.562	0.0433
Differentiation			0.0043			0.0390
Well	0.936	0.798–1.099	0.4194	1.012	0.852–1.202	0.8959
Moderately	Reference			Reference		
Poorly	1.192	1.066–1.332	0.0020	1.131	1.007–1.271	0.0378
Undifferentiated	1.220	0.939–1.586	0.1373	1.157	0.840–1.594	0.3715
Unknown	1.053	0.879–1.263	0.5746	1.049	0.868–1.266	0.6226
Number of lymph nodes examined			< 0.0001			0.0001
0	Reference			Reference		
1–10	0.654	0.563–0.760	< 0.0001	0.726	0.610–0.864	0.0003
11–20	0.580	0.489–0.688	< 0.0001	0.651	0.534–0.795	< 0 .0001
> 20	0.515	0.411–0.645	< 0.0001	0.583	0.454–0.749	< 0.0001
Unknown‡	0.634	0.517–0.777	< 0.0001	0.728	0.580–0.908	0.0050
Year of diagnosis			0.0359			0.0475
2004–2009	Reference			Reference		
2010–2015	0.887	0.792–0.992	0.0359	0.879	0.773–0.997	0.0475

Table 2 Continued

Characteristic	Univariate			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Surgery type			< 0.0001			0.0024
Sublobar resection	1.435	1.264–1.629	< 0.0001	1.283	1.103–1.494	0.0013
Lobectomy	Reference			Reference		
Pneumonectomy	1.159	0.993–1.354	0.0617	1.142	0.969–1.345	0.1141
ACT use			0.0359			0.0232
Without	Reference			Reference		
With	0.900	0.816–0.993	0.0359	0.882	0.792–0.983	0.0232
PORT use			< 0.0001			< 0.0001
Without	Reference			Reference		
With	1.606	1.418–1.818	< 0.0001	1.686	1.470–1.934	< 0.0001

†First quantile denotes the most county attributes. ‡Lymph nodes were examined but the exact number is unknown. ACT, adjuvant chemotherapy; CI, confidence interval; HR, hazard ratio; PORT, postoperative radiation therapy.

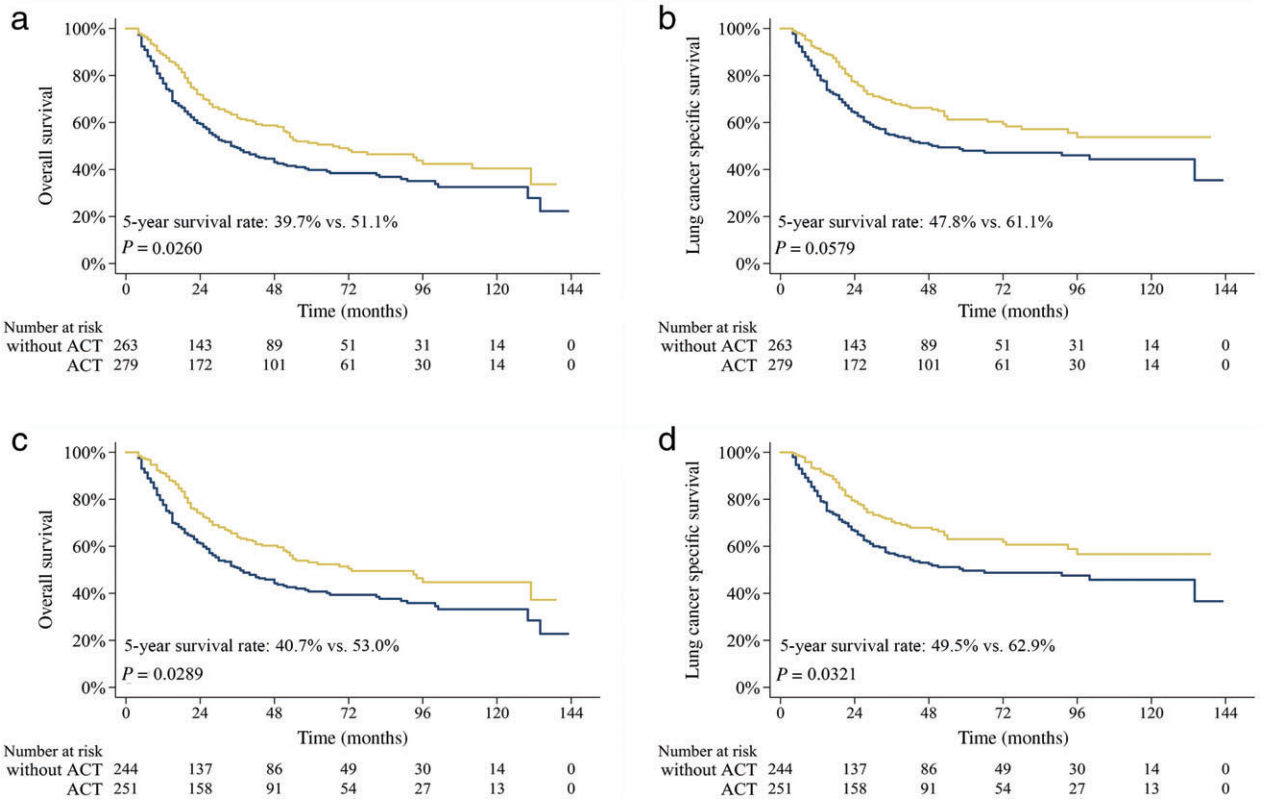

Figure 1 Survival curves for patients with tumors > 7 cm and aged 21–65 years after matching. (**a**) Overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) curves of the entire cohort. (**c**) OS and (**d**) LCSS curves of patients who did not receive postoperative radiation therapy (PORT). ACT, adjuvant chemotherapy. (——) Without ACT and (——) ACT.

this class, the results did not significantly change (5-year OS 40.7% vs. 53.0%, $P = 0.0289$; 5-year LCSS 49.5% vs. 62.9%, $P = 0.0321$) (Fig 1). However, in patients aged > 65 with tumors 0–7 cm, the LCSS in the group administered ACT appeared to be poorer, although there was no statistically significant difference. In the entire cohort, LCSS was 54.6% versus 51.5% ($P = 0.4658$), while it was 59.0% versus 53.3% ($P = 0.6394$) when the analysis was limited to patients not did not receive ACT PORT (Figure S3). We did not perform survival comparison between patients who received PORT with patients who did or did not receive ACT in the matched analysis

because the rate of radiation use in operable N0 patients was too low to allow a sufficiently large sample for a paired z-test.

IPTW Cox analysis showed similar results to the matched analysis for both the entire cohort and in patients who did not receive PORT; ACT was a prognostic protective factor, specifically for patients with tumors > 7 cm and aged > 65 (hazard ratio [HR] range: 0.579–0.928 for death from any cause and 0.557–0.939 for death from lung cancer) (Figs 2, 3). Statistical differences were also observed in a limited number of patients aged 21–65 with 0–7 cm tumors and who received PORT (HR range: 0.251 –0.684 for death from any cause and 0.191–0.552 for death from lung cancer).

It is worth noting that there was a proportion of tumors in our study dataset (12%) > 7 cm that invaded the superior sulcus; chemotherapy is specifically recommended for these tumors.[6] Therefore, when secondary analyses were performed, we limited the sample to patients aged 21–65 with tumors >7 cm using reselected covariates that

Model	No. of events/total no. (%)		IPTW based on PS
	without ACT	ACT	Hazard Ratio(95% CI)
Stratified analysis			
size≤7cm , aged≤65			
Entire cohort	126/263(47.91%)	127/272(46.69%)	0.924(0.728-1.174)
Limited to PORT use	10/14(71.43%)	48/79(60.76%)	0.414(0.251-0.684)
Limited to non- PORT use	116/249(46.59%)	79/193(40.93%)	0.934(0.706-1.234)
size≤7cm , aged>65			
Entire cohort	349/577(60.49%)	160/275(58.18%)	0.956(0.790-1.157)
Limited to PORT use	38/54(70.37%)	55/80(68.75%)	0.797(0.512-1.240)
Limited to non- PORT use	311/523(59.46%)	105/195(53.85%)	0.938(0.750-1.173)
size>7cm , aged≤65			
Entire cohort	177/294(60.20%)	192/435(44.14%)	0.756(0.616-0.928)
Limited to PORT use	13/19(68.42%)	64/106(60.38%)	1.370(0.596-3.147)
Limited to non- PORT use	164/275(59.64%)	128/329(38.91%)	0.727(0.579-0.913)
size>7cm , aged>65			
Entire cohort	351/562(62.46%)	183/330(55.45%)	0.977(0.819-1.165)
Limited to PORT use	28/37(75.68%)	50/66(75.76%)	0.724(0.455-1.152)
Limited to non- PORT use	323/525(61.52%)	133/264(50.38%)	0.959(0.790-1.164)
size>7cm , aged≤65 adiusted for ss			
Entire cohort	177/294(60.20%)	192/435(44.14%)	0.739(0.602-0.907)
Limited to PORT use	13/19(68.42%)	64/106(60.38%)	1.231(0.541-2.801)
Limited to non- PORT use	164/275(59.64%)	128/329(38.91%)	0.704(0.560-0.884)

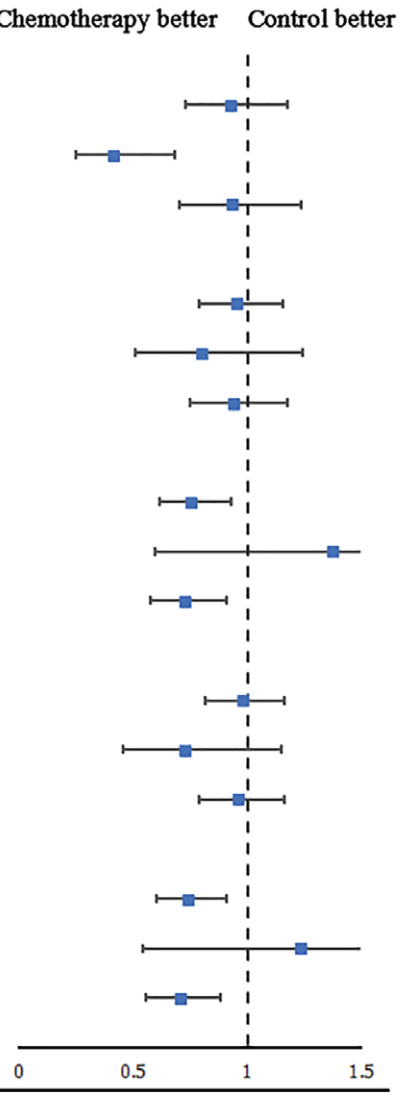

Figure 2 Results of Cox model adjusting for inverse probability of treatment weighting (IPTW) based on propensity score (overall survival). ACT, adjuvant chemotherapy; CI, confidence interval; event, dead of any cause; PORT, postoperative radiation therapy; PS, propensity score; SS superior sulcus.

included the extent of superior sulcus invasion in a PS model. We observed that treatment with ACT still correlated with significantly improved survival after adjusting for the extent of superior sulcus invasion (entire cohort: 5-year OS 41.9% vs. 52.5%, $P = 0.0003$; 5-year LCSS 49.8% vs. 61.8%, $P = 0.0005$; limited to non-PORT patients: 5-year OS 43.1% vs. 53.2%, $P = 0.0001$; 5-year LCSS 51.6% vs. 62.4%, $P = 0.0002$) (Fig S5). IPTW Cox analysis also correlated with the results of the matched analysis (HR range: 0.560–0.907 for death from any cause and 0.539–0.909 for death from lung cancer) (Figs 2, 3).

Discussion

ACT has been reported to be a protective prognostic factor in resected NSCLC.[23] Chemotherapy followed by surgery in selected patients may contribute to the downstaging of tumors in addition to prolonged survival.[24] Revision of the

Model	No. of events/total no. (%)		IPTW based on PS
	without ACT	ACT	Hazard Ratio(95% CI)
Stratified analysis			
size≤7cm , aged≤65			
Entire cohort	90/263(34.22%)	95/272(34.93%)	0.860(0.654-1.132)
Limited to PORT use	9/14(64.29%)	36/79(45.57%)	0.325(0.191-0.552)
Limited to non- PORT use	81/249(32.53%)	59/193(30.57%)	0.937(0.674-1.302)
size≤7cm , aged>65			
Entire cohort	210/577(36.40%)	123/275(44.73%)	1.156(0.922-1.449)
Limited to PORT use	29/54(53.70%)	38/80(47.50%)	0.784(0.466-1.318)
Limited to non- PORT use	181/523(34.61%)	85/195(43.59%)	1.222(0.938-1.593)
size>7cm , aged≤65			
Entire cohort	139/294(47.28%)	147/435(33.79%)	0.716(0.569-0.902)
Limited to PORT use	13/19(68.42%)	50/106(47.17%)	1.118(0.482-2.594)
Limited to non- PORT use	126/275(45.82%)	97/329(29.48%)	0.723(0.557-0.939)
size>7cm , aged>65			
Entire cohort	242/562(43.06%)	147/330(44.55%)	1.074(0.876-1.317)
Limited to PORT use	24/37(64.86%)	40/66(60.61%)	0.679(0.415-1.110)
Limited to non- PORT use	218/525(41.52%)	107/264(40.53%)	1.106(0.884-1.384)
size>7cm , aged≤65 adjusted for ss			
Entire cohort	139/294(47.28%)	147/435(33.79%)	0.702(0.557-0.885)
Limited to PORT use	13/19(68.42%)	50/106(47.17%)	1.006(0.438-2.310)
Limited to non- PORT use	181/523(34.61%)	85/195(43.59%)	0.700(0.539-0.909)

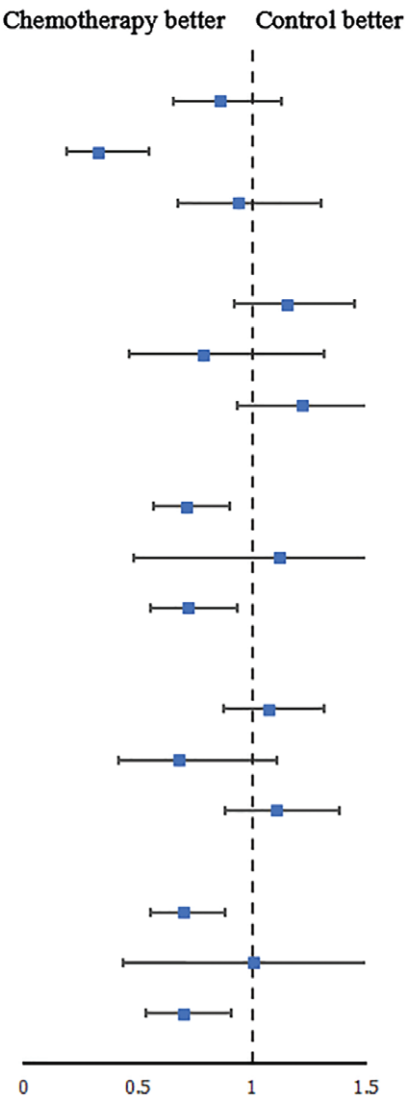

Figure 3 Results of Cox model adjusting for inverse probability of treatment weighting (IPTW) based on propensity score (lung cancer specific survival). ACT, adjuvant chemotherapy; CI, confidence interval; event, dead of any cause; PORT, postoperative radiation therapy; PS, propensity score; SS, superior sulcus.

TNM staging systems has been a major concern when analyzing treatment strategies for NSCLC. Early in the sixth staging classification, clinical trials had evaluated the effect of ACT in operable stage III patients and showed improved five-year survival of up to 35%.[10,23,25] However, analyses specifically for T4 (stage IIIB) tumors are limited, and the majority of participants in the trials were aged < 65. In a population-based study focused on elderly patients with T4 N0–1 NSCLCs, there was no survival improvement and severe adverse events were observed; in addition, tumors had been revised as stage IIIA in the seventh edition TNM staging systems.[10] Our analysis did not show any benefit of ACT in elderly patients, which was consistent with the latter study. The five-year OS rates in the elderly patients in our study ranged from 39.4% to 46.7% in the adjuvant treatment group and 35.8% to 43.7% in the placebo group, which were slightly higher than in earlier reports because we included only N0 patients who had undergone surgical resection and were more recently diagnosed with NSCLC, as well as whose life status was significantly better than those with N1–N2 stage IIIA.

The NCCN Guidelines indicate that tumor size should be considered when administering chemotherapy.[6] Evidence has shown the influence of tumor size on ACT. The JBR.10 trial noted a survival benefit of chemotherapy in stage IB or II patients with tumors ≥ 4 cm.[8] Another study suggested that the effect of chemotherapy appeared to increase with tumor size.[26] Our study found that ACT significantly improved survival in patients aged 21–65 with > 7 cm tumors who did not receive PORT, which supported results showing improvement in survival in patients with tumors > 7 cm.[26] Differing from the outcomes of these studies, however, our matched analysis showed no significant prognostic effect of ACT for tumors ≤ 7 cm, even in patients aged < 65. Different findings may result from the differences in tumor staging classifications, as our study included patients with T4N0 based on the eighth edition.

In IPTW analysis, ACT did not provide a survival benefit for the majority of patients administered PORT. This outcome was consistent with the results of a randomized trial initiated by the Eastern Cooperative Oncology Group.[27] A meta-analysis reported that PORT was detrimental to pN0-1 patients.[28] The use of chemotherapy alone rather than chemoradiotherapy is preferred by some oncologists, but PORT is feasible if not administered prior to surgery.[6] However, it has been shown that patients aged 21–65 with 0–7 cm T4 tumors administered PORT may potentially benefit from ACT. PORT may be effective in patients with positive margins or those who are upstaged N2 after surgery.[29] Further analyses with a larger study population are required to verify these results, as only 14 cases in the placebo group were included in this class (Figs 2,3).

Our study had certain strengths and limitations that should be noted. First, we identified nationally representative data from the SEER registry. Second, we referred to the eighth edition TNM staging system and focused on T4N0 cases, the clinical care of which has provoked lasting conflict. Because T3 tumors > 7 cm have been redefined as T4, we had a liberal quantity of cases for use in stratification analysis. Additionally, we used PSM and IPTW to minimize confounding bias, directly estimated treatment effect, and compared the outcomes of these two statistical methods. During survival analysis, a longer follow-up period may result in time-dependent covariates being included in the confounding (exposure) factors.[20,30] However, the SEER registry does not include information from Medicare claims; thus, we have no data on the specific chemotherapy regimens and comorbidity scores, which are part of the clinical assessment of cancer patients. Although the Medicare-linked registry includes more details regarding treatment and comorbidities than the SEER database, younger patients may be registered under diseases other than lung cancer.[31] In addition, our analysis data were mainly from white people; according to the NCCN Guidelines, *EGFR* mutations are related to the choice of treatment plan and *EGFR* mutation prevalence is associated with race.[32,33] Because the SEER database does not contain genetic detection information, the application of the conclusions of our study for all patients is probably limited and requires further investigation. Finally, as previously mentioned, a portion of 0–7 cm tumors should be upgraded from T3 to T4, except for anatomic structures adjacent to the mediastinum; excluding these cases would probably influence the use of our results for all T4N0 NSCLC patients.

In summary, this study specified a group of resected patients aged 21–65 with tumors > 7 cm not administered PORT. These patients could benefit from ACT. The value of chemotherapy combined with PORT for the treatment of T4N0 disease requires further examination.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Figure S1. Flow diagram of the selection process for the study cohort. ACT, adjuvant chemotherapy; NSCLC, non-small cell lung cancer; PORT, postoperative radiation therapy. ICD-O-3 histology code ranges: adenocarcinoma (8140–8141, 8143, 8147, 8255, 8260, 8310, 8430, 8480–8481, 8490, 8571–8575); bronchioalveolar carcinoma (8250–8254); large cell carcinoma (8012–8013); squamous cell carcinoma (8050, 8052, 8070–8076,8078, 8082–8084); and adenocarcinoma with mixed subtype (8046, 8010, 8020, 8560, 8570).

Figure S2. Survival curves of patients aged 21–65 years with tumors 0–7 cm after matching. (**a**) Overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) curves of the entire cohort. (**c**) OS and (**d**) LCSS of patients who did not receive postoperative radiation therapy (PORT). ACT, adjuvant chemotherapy.

Figure S3. Survival curves of patients aged > 65 years with tumors 0–7 cm after matching. **a**) Overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) curves of the entire cohort. (**c**) OS and (**d**) LCSS of patients who did not receive postoperative radiation therapy (PORT). ACT, adjuvant chemotherapy.

Figure S4. Survival curves of patients aged > 65 with tumors > 7 cm after matching. (**a**) Overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) curves of the entire cohort. (**c**) OS and (**d**) LCSS of patients who did not receive postoperative radiation therapy (PORT). ACT, adjuvant chemotherapy.

Figure S5. Survival curves for superior sulcus adjusted analysis of patients aged 21–65 with tumors > 7 cm after matching. (**a**) Overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) curves of the entire cohort. (**c**) OS and (**d**) LCSS of patients who did not receive postoperative radiation therapy (PORT). ACT, adjuvant chemotherapy.

Table S1. Baseline characteristics of the virtual sample generated by inverse probability of treatment weighting

