PROGNOSTIC VALUE OF ADJUVANT THERAPY IN T4 NON-SMALL CELL LUNG CANCER: AN INVERSE PROBABILITY OF TREATMENT WEIGHTING ANALYSIS

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Keywords
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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
Patients diagnosed at autopsy or on their death certificate were reclassified as T4N0M0 based on the eighth TNM staging system. 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 \( (P < 0.20) \), 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. 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
| Characteristic                        | Before matching | After matching | P     | SMD†(%) |
|--------------------------------------|-----------------|----------------|-------|---------|
|                                      | No ACT (n = 1696) | ACT (n = 1312) |       |         |
| Age, years                           | 70              | 65             | < 0.0001 | -2.33  |
| Median                               | 70              | 65             | < 0.0001 | -2.33  |
| Range                                | 25–94           | 28–88          |       |         |
| Tumor size, cm                       | 7.1             | 7.5            | < 0.0001 | 2.60   |
| Median                               | 7.1             | 7.5            | < 0.0001 | 2.60   |
| Range                                | 0.2–18.4        | 0.4–23.0       |       |         |
| Gender, N (%)                        | 957 (56.43%)    | 752 (57.32%)   | 0.6250 | 1.19   |
| Male                                 | 957 (56.43%)    | 752 (57.32%)   | 0.6250 | 1.19   |
| Female                               | 739 (43.57%)    | 560 (42.68%)   | 0.6013 | -2.23  |
| Race, N (%)                          | 1439 (84.85%)   | 1083 (82.55%)  | 0.0376 | -0.79  |
| White                                | 966 (56.84%)    | 803 (61.20%)   | 0.0159 | -2.27  |
| Black                                | 149 (8.79%)     | 152 (11.58%)   | 1.59   |         |
| Black                                | 149 (8.79%)     | 152 (11.58%)   | 1.59   |         |
| Other                                | 108 (6.36%)     | 77 (5.87%)     | 0.6013 | -2.23  |
| Marital status, N (%)                | 964 (56.84%)    | 803 (61.20%)   | 0.0159 | -2.27  |
| Married                              | 964 (56.84%)    | 803 (61.20%)   | 0.0159 | -2.27  |
| Unmarried                            | 732 (43.16%)    | 509 (38.80%)   | 0.7867 | -0.83  |
| Insurance, N (%)                     | 1115 (65.74%)   | 961 (73.25%)   | < 0.0001 | 0.65   |
| Insured                              | 1115 (65.74%)   | 961 (73.25%)   | < 0.0001 | 0.65   |
| County attributes in education, N (%)|                 |                |       |         |
| First quantile‡                      | 428 (25.24%)    | 347 (26.45%)   | 0.5011 | 0.5906 |
| Second quantile                      | 434 (25.59%)    | 320 (24.39%)   | 0.2271 | -0.22  |
| Third quantile                       | 410 (24.17%)    | 335 (25.53%)   | 0.0016 | -0.98  |
| Fourth quantile                      | 424 (25.00%)    | 310 (23.63%)   | 0.0016 | -0.98  |
| County attributes in median family income, N (%) |       |                |       |         |
| First quantile‡                      | 433 (25.53%)    | 362 (27.59%)   | 0.0235 | 5.02   |
| Second quantile                      | 438 (25.83%)    | 340 (25.91%)   | 0.2271 | -0.22  |
| Third quantile                       | 384 (22.64%)    | 292 (22.26%)   | 0.0016 | -0.98  |
| Fourth quantile                      | 441 (26.00%)    | 318 (24.24%)   | 0.0016 | -0.98  |
| Location, n (%)                      | 879 (51.83%)    | 699 (53.28%)   | 0.7843 | 2.78   |
| Upper lobe                           | 879 (51.83%)    | 699 (53.28%)   | 0.7843 | 2.78   |
| Middle lobe                          | 68 (4.01%)      | 48 (3.66%)     | 0.357 | 1.06   |
| Lower lobe                           | 588 (34.67%)    | 436 (33.23%)   | 0.357 | 1.06   |
| Main bronchus, Other                 | 161 (9.49%)     | 128 (9.83%)    | 1.002 | 2.02   |
| Laterality, N (%)                    | 676 (39.86%)    | 532 (40.55%)   | 0.7018 | 0.6822 |
| Left                                 | 676 (39.86%)    | 532 (40.55%)   | 0.7018 | 0.6822 |
| Right                                | 1020 (60.14%)   | 780 (59.45%)   | 0.7018 | 0.6822 |
| Histology, N (%)                     | 736 (43.40%)    | 634 (48.32%)   | 0.0016 | -0.98  |
| Adenocarcinoma                       | 736 (43.40%)    | 634 (48.32%)   | 0.0016 | -0.98  |
| Bronchioalveolar carcinoma           | 207 (12.20%)    | 104 (7.93%)    | 0.8833 | 2.73   |
| Large cell carcinoma                 | 67 (3.95%)      | 56 (4.27%)     | 0.357 | 1.06   |
| Squamous cell                        | 552 (32.55%)    | 415 (31.63%)   | 0.357 | 1.06   |
| Adenocarcinoma with mixed subtype    | 134 (7.90%)     | 103 (7.85%)    | 0.0016 | -0.98  |
| Differentiation, N (%)               | 258 (15.21%)    | 160 (12.20%)   | 0.0044 | 0.00   |
| Well                                 | 258 (15.21%)    | 160 (12.20%)   | 0.0044 | 0.00   |
| Moderately                            | 614 (36.20%)    | 446 (33.99%)   | 0.357 | 1.06   |
| Poorly                                | 614 (36.20%)    | 446 (33.99%)   | 0.357 | 1.06   |
| Undifferentiated                     | 59 (3.48%)      | 40 (3.05%)     | 0.357 | 1.06   |
| Unknown                               | 151 (8.91%)     | 105 (8.00%)    | 0.357 | 1.06   |

Table 1 Baseline characteristics of T4N0M0 non-small cell lung cancer patients before and after propensity score matching.
covariables is independent of the processing allocation. 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). 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 ($P = 0.0235$), 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

| Characteristic                                | Univariate                  |          |          | Multivariable     |          |          |
|-----------------------------------------------|-----------------------------|---------|---------|-------------------|---------|---------|
|                                               | 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 | 0.407 | 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                   |         |         | 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                   |         |         | 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                   |         |         | 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                               | 0.0434 |            |        | 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                                            | 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 |
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.

Table 2

| Characteristic          | Univariate HR 95% CI | \( P \) | Multivariable HR 95% CI | \( P \) |
|-------------------------|----------------------|--------|-------------------------|--------|
| Surgery type            |                      |        |                         |        |
| 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                 |                      |        |                         |        |
| Without                 | Reference            |        | Reference               |        |
| With                    | 0.900 0.816–0.993    | 0.0359 | 0.882 0.792–0.983        | 0.0232 |
| PORT use                |                      |        |                         |        |
| 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.
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. Therefore, when secondary analyses were performed, we limited the sample to patients aged 21–65 with tumors >7 cm using reselected covariates that

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**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.\(^2\) Chemotherapy followed by surgery in selected patients may contribute to the downstaging of tumors in addition to prolonged survival.\(^2\)\(^4\) Revision of the
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%. 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. 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. Evidence has shown the influence of tumor size on ACT. The JBRI 10 trial noted a survival benefit of chemotherapy in stage IB or II patients with tumors ≥ 4 cm. Another study suggested that the effect of chemotherapy appeared to increase with tumor size. 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. 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. A meta-analysis reported that PORT was detrimental to pN0-1 patients. The use of chemotherapy alone rather than chemoradiotherapy is preferred by some oncologists, but PORT is feasible if not administered prior to surgery. 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. 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.

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. 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. In addition, our data analysis 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. 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 Information may 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.