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Postoperative radiotherapy for stage pIIIA-N2 non-small cell lung cancer patients undergoing sublobar resection

A retrospective cohort study

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Abstract

This study assesses the effect of postoperative radiotherapy on survival outcomes in patients diagnosed with stage pIIIA-N2 non-small cell lung cancer (NSCLC) after sublobar resection. Data of patients with stage pIIIA-N2 NSCLC who underwent sublobar resection were extracted from the Surveillance, Epidemiology, and End Results database spanning from 2000 to 2020. Patients were divided into 2 groups: postoperative radiotherapy and observation. Cancer-specific survival (CSS) and overall survival (OS) were analyzed and compared between the 2 groups. A total of 444 patients were included in the study, with 210 (47.3%) receiving postoperative radiotherapy and 234 (52.7%) with observation. The CSS (hazard ratio [HR] = 0.99, 95% confidence interval [CI]: 0.78–1.26; $P = .926$) and OS (HR = 0.93, 95% CI: 0.75–1.15; $P = .512$) did not show significant differences between the postoperative radiotherapy and observation groups. Subgroup analysis of patients receiving postoperative chemotherapy revealed comparable CSS (HR = 1.24, 95% CI: 0.89–1.71; $P = .203$) and OS (HR = 1.12, 95% CI: 0.85–1.49; $P = .425$) between the 2 groups. Similarly, for patients without postoperative chemotherapy, CSS (HR = 1.11, 95% CI: 0.66–1.84; $P = .699$) and OS (HR = 1.08, 95% CI: 0.68–1.71; $P = .740$) were not significantly different between the 2 groups. Postoperative radiotherapy does not improve survival in patients with stage pIIIA-N2 NSCLC following sublobar resection.

Abbreviations: CI = confidence interval, CSS = disease-free survival, HR = hazard ratio, NSCLC = non-small cell lung cancer, OS = overall survival, SEER = the surveillance, epidemiology, and end results.

Keywords: non-small cell lung cancer, postoperative radiotherapy, stage pIIIA-N2, sublobar resection

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for an estimated 1.6 million deaths annually.[1,2] Non-small cell lung cancer (NSCLC) comprises approximately 85% of all lung cancer cases, with adenocarcinoma and squamous cell carcinoma being the predominant histological subtypes.[3] Over the past 2 decades, advances in diagnostic imaging and the implementation of lung cancer screening programs have significantly improved the detection and staging of early-stage NSCLC. For patients with early-stage disease, lobectomy is considered the standard of care.[4]

The landmark 1995 study by the Lung Cancer Study Group demonstrated that sublobar resection was inferior to lobectomy for early-stage NSCLC, particularly for tumors larger than 2 cm, which led to the widespread adoption of lobectomy as the standard treatment.[5] However, recent pivotal trials have questioned this long-held view, especially for small peripheral NSCLC lesions. The Japanese Clinical Oncology Group/West Japan Oncology Group (JCOG0802/WJOG4607L) and the Cancer and Leukemia Group B (CALGB140503) trials have provided compelling evidence that sublobar resection is effective for peripheral lung cancers measuring ≤ 2 cm.[6,7] Notably, the JCOG0802/WJOG4607L trial showed a survival benefit for sublobar resection, suggesting that preserving lung parenchyma offers advantages, such as better postoperative pulmonary function and reduced morbidity.[6] Furthermore, the JCOG1211 trial extended the potential indication for sublobar resection to tumors up to 3 cm in size, particularly those with a ground-glass opacity dominant feature, which is associated with a less aggressive clinical course.[8] As a result, sublobar resection has increasingly been adopted in clinical practice for patients with early-stage NSCLC.

However, some patients who undergo sublobar resection may later be diagnosed with stage pIIIA-N2 disease.[9] In the context

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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of stage pIIIA-N2 NSCLC following lobectomy, postoperative chemotherapy has been shown to improve both disease-free survival and overall survival (OS) in patients with completely resected tumors.[10–12] In contrast, several clinical trials and retrospective studies have suggested that postoperative radiotherapy does not confer any additional benefit in terms of disease-free survival or OS.[13–17] This raises the question of whether postoperative radiotherapy is necessary for patients with stage pIIIA-N2 disease following sublobar resection. The aim of this retrospective cohort study is to compare survival outcomes between postoperative radiotherapy and observation in stage pIIIA-N2 NSCLC patients who undergo sublobar resection.

2. Materials and methods

2.1. Patients

This study analyzed patients with lung squamous cell carcinoma and adenocarcinoma from the surveillance, epidemiology, and end results (SEER) program between 2000 and 2020. Data were retrieved using the SEER*Stat software, version 8.4.1.[18] SEER (Medical Center Drive, Bethesda) is a publicly available database containing de-identified data; thus, ethical review was not required. The Institutional Review Board of Guangxi Medical University Cancer Hospital waived the need for formal ethical approval for this study.

We included patients with histologically confirmed stage pIIIA-N2 NSCLC who underwent sublobar resection. Exclusion criteria comprised patients who received preoperative radiotherapy, neoadjuvant chemotherapy, or underwent lobectomy. Collected clinical variables included demographic details (age, sex, race), tumor characteristics (primary site, laterality, grade, histology, T stage), and treatment data (chemotherapy and radiotherapy). Based on the administration of postoperative radiotherapy, patients were divided into 2 groups: the postoperative radiotherapy group and the observation group.

2.2. Statistical analysis

Age was categorized based on the median value. Categorical variables, including age, sex, race, primary tumor site, tumor location, grade, histology, T stage, and chemotherapy status, were compared between the postoperative radiotherapy and observation groups using the χ^2 test or Fisher exact test, as appropriate, based on data distribution. Statistical analyses were conducted using SPSS Statistics Version 26.0 (IBM Corp., Armonk).

Cancer-specific survival (CSS) and OS were evaluated between the postoperative radiotherapy and observation groups using Kaplan–Meier survival curves. Log-rank tests were performed to assess statistical significance of survival differences between the groups. Statistical analyses were conducted using R software (version 4.4.0). A 2-tailed *P*-value of <.05 was considered statistically significant. To identify independent prognostic factors influencing CSS and OS, multivariable Cox regression analysis was performed, adjusting for all relevant clinical parameters.

Subgroup analysis was performed based on postoperative chemotherapy status. Patients who received postoperative chemotherapy were further divided into 2 groups based on whether they received postoperative radiotherapy or not. Similarly, patients who did not receive postoperative chemotherapy were also categorized into radiotherapy and observation groups. CSS and OS between these subgroups were compared using Kaplan–Meier methods and log-rank tests.

3. Results

3.1. Patient characteristics

A total of 444 patients were included in this study. Of these, 210 (47.3%) patients were in the postoperative radiotherapy group, while 234 (52.7%) patients were in the observation group. Table 1 provides a summary of the clinical characteristics for the 2 groups.

Table 1

Patient characteristics.

	Observation (n = 234)	Radiotherapy (n = 210)	*P*
Age			
≤69	97 (41.5%)	126 (60.0%)	<.001
>69	137 (58.5%)	84 (40.0%)	
Sex			
Female	120 (51.3%)	107 (51.0%)	.999
Male	114 (48.7%)	103 (49.0%)	
Race			
White	209 (89.3%)	179 (85.2%)	.341
Black	13 (5.6%)	19 (9.1%)	
Others	12 (5.1%)	12 (5.7%)	
Site			
Upper lobe	128 (54.7%)	131 (62.4%)	.017
Middle lobe	10 (4.3%)	10 (4.8%)	
Lower lobe	89 (38.0%)	54 (25.7%)	
Others	7 (3.0%)	15 (7.1%)	
Laterality			
Left	109 (46.6%)	108 (51.4%)	.355
Right	125 (53.4%)	102 (48.6%)	
Grade			
I/II	109 (46.6%)	85 (40.5%)	.411
III/IV	99 (42.3%)	101 (48.1%)	
Unknown	26 (11.1%)	24 (11.4%)	
Histology			
Squamous cell carcinoma	177 (75.6%)	151 (71.9%)	.432
Adenocarcinoma	57 (24.4%)	59 (28.1%)	
T stage			
T1	124 (53.0%)	106 (50.5%)	.664
T2	110 (47.0%)	104 (49.5%)	
Chemotherapy			
No	129 (55.1%)	26 (12.4%)	<.001
Yes	105 (44.9%)	184 (87.6%)	

The factors of sex, race, laterality, tumor grade, histology, and T stage were well balanced between the 2 groups. However, significant differences were observed in age, primary tumor site, and chemotherapy status. Specifically, the postoperative radiotherapy group had a higher proportion of patients aged ≤ 69 years, tumors located in the upper lobes, and those who received postoperative chemotherapy.

3.2. Cancer-specific survival

The median CSS for the postoperative radiotherapy group was 43 months, compared to 40 months for the observation group. There was no statistically significant difference in CSS between the 2 groups (hazard ratio [HR] = 0.99, 95% confidence interval [CI]: 0.78–1.26; *P* = .926, Fig. 1A). Multivariable proportional hazards regression analysis further confirmed that postoperative radiotherapy was not an independent prognostic factor for CSS (HR = 1.18, 95% CI: 0.89–1.56; *P* = .257, Fig. 1B).

3.3. Overall survival

The median OS for the postoperative radiotherapy group was 36.5 months, compared to 30 months for the observation group. The difference in OS between the 2 groups was not statistically significant (HR = 0.93, 95% CI = 0.75–1.15; *P* = .512, Fig. 2A). Multivariable proportional hazards regression analysis also indicated that postoperative radiotherapy did not serve as an independent prognostic factor for OS (HR = 1.10, 95% CI = 0.86–1.41; *P* = .443, Fig. 2B).

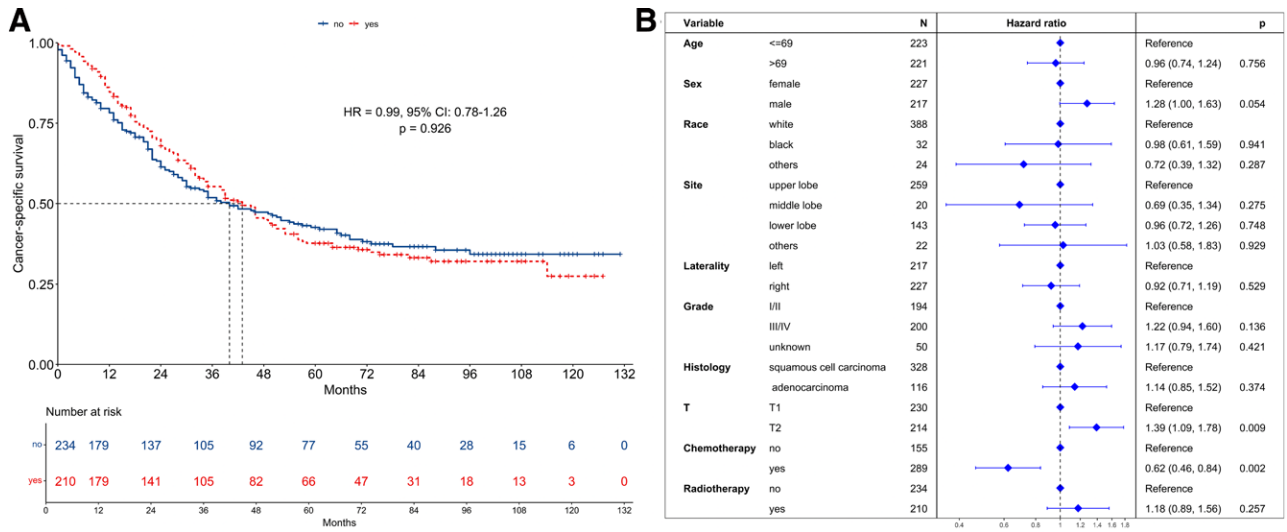

Figure 1. Cancer-specific survival of the entire group. (A) Kaplan–Meier survival curve between postoperative radiotherapy and observation. (B) Multivariable proportional hazards regression analysis of cancer-specific survival.

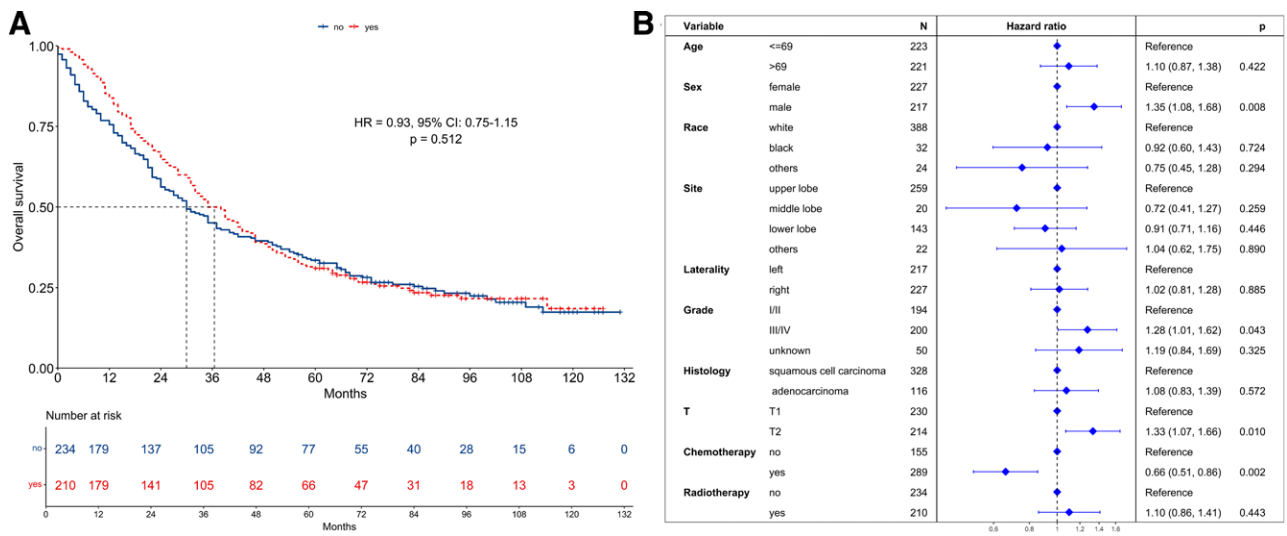

Figure 2. Overall survival of the entire group. (A) Kaplan–Meier survival curve between postoperative radiotherapy and observation. (B) Multivariable proportional hazards regression analysis of overall survival.

3.4. Subgroup analysis of patients with postoperative chemotherapy

In the subgroup of patients who received postoperative chemotherapy, the median CSS was 46 months for those in the postoperative radiotherapy group, compared to 55 months in the observation group. No significant difference in CSS was found between these 2 groups (HR = 1.24, 95% CI = 0.89–1.71; P = .203, Fig. 3A). Multivariable proportional hazards regression confirmed that postoperative radiotherapy was not an independent prognostic factor for CSS in this subgroup (HR = 1.25, 95% CI = 0.89–1.77; P = .204, Fig. 3B).

The median OS in this subgroup was 39 months for the postoperative radiotherapy group, compared to 40 months for the observation group. There was no significant difference in OS between these groups (HR = 1.12, 95% CI = 0.85–1.49; P = .425, Fig. 4A). Multivariable proportional hazards regression analysis further confirmed that postoperative radiotherapy was not an independent prognostic factor for OS in this subgroup (HR = 1.16, 95% CI = 0.86–1.57; P = .327, Fig. 4B).

3.5. Subgroup analysis of patients without postoperative chemotherapy

In the subgroup of patients who did not receive postoperative chemotherapy, the median CSS was 26 months for the postoperative radiotherapy group, compared to 29 months for the observation group. Again, no significant difference in CSS was observed between the groups (HR = 1.11, 95% CI = 0.66–1.84; P = .699, Fig. 5A). Multivariable proportional hazards regression analysis confirmed that postoperative radiotherapy was not an independent prognostic factor for CSS in this subgroup (HR = 0.97, 95% CI = 0.76–1.25; P = .831, Fig. 5B).

The median OS in this subgroup was 25 months for the postoperative radiotherapy group, compared to 26 months for the observation group. There was no significant difference in OS between the groups (HR = 1.08, 95% CI = 0.68–1.71; P = .740, Fig. 6A). Similarly, multivariable proportional hazards regression analysis indicated that postoperative radiotherapy was not an independent prognostic factor for OS in this subgroup (HR = 0.94, 95% CI = 0.75–1.17; P = .577, Fig. 6B).

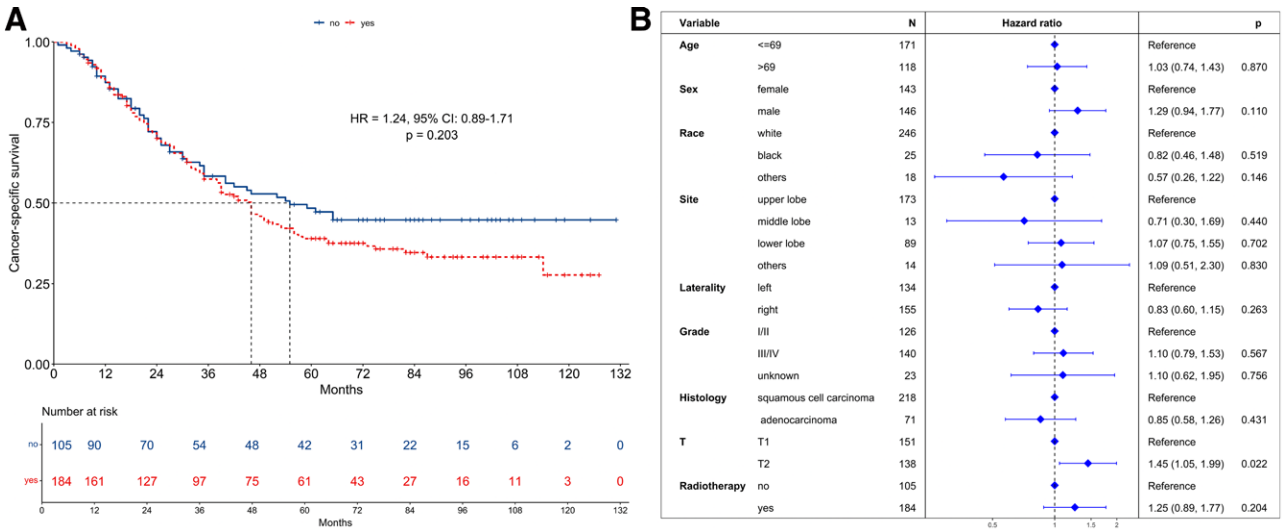

Figure 3. Cancer-specific survival of patients with postoperative chemotherapy. (A) Kaplan–Meier survival curve between postoperative radiotherapy and observation. (B) Multivariable proportional hazards regression analysis of cancer-specific survival.

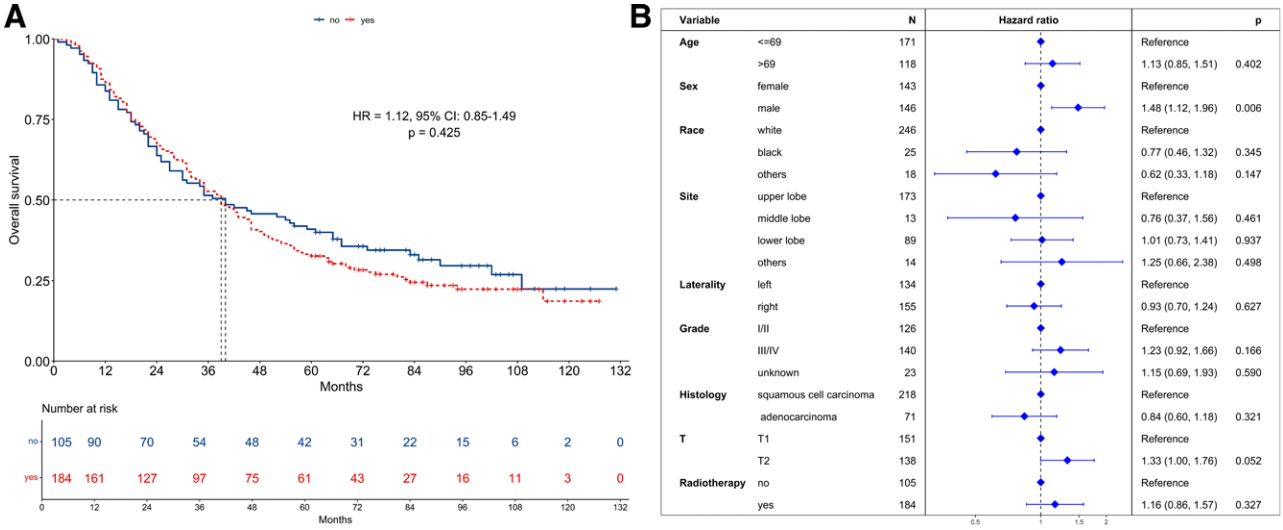

Figure 4. Overall survival of patients with postoperative chemotherapy. (A) Kaplan–Meier survival curve between postoperative radiotherapy and observation. (B) Multivariable proportional hazards regression analysis of overall survival.

4. Discussion

This study demonstrates that postoperative radiotherapy does not significantly improve CSS or OS in patients with stage pIIIA-N2 NSCLC following sublobar resection. These findings further support the recommendation against the routine use of postoperative radiotherapy for stage pIIIA-N2 NSCLC, even in cases where radical lobectomy was not performed.

The cumulative rates of locoregional recurrence in patients with stage pIIIA-N2 NSCLC have been reported to range from 20% to 60%.[19–21] However, the Lung ART trial demonstrated that while postoperative radiotherapy improved locoregional control rates, it did not translate into an overall survival benefit.[13] Similarly, the PORT-C trial conducted in China, despite variations in radiotherapy techniques, doses, and the use of postoperative chemotherapy, yielded consistent results.[14] Furthermore, a systematic review and meta-analysis also concluded that postoperative radiotherapy did not improve median disease-free survival.[16] These studies have indicated that postoperative radiotherapy does not enhance OS in patients with stage pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy.

It is crucial to acknowledge that stage pIIIA-N2 NSCLC is a heterogeneous disease group. While postoperative radiotherapy did not improve OS across the entire cohort of stage pIIIA-N2 NSCLC, certain subgroups of patients with poor prognostic factors might still benefit from this treatment.[22,23] A retrospective cohort study focused on identifying high-risk patients based on the lymph node ratio found that postoperative radiotherapy did not significantly affect CSS or OS, even in high-risk patients.[17] These findings further suggest that postoperative radiotherapy should not be routinely recommended for stage pIIIA-N2 NSCLC patients, including those considered high-risk. Our results are in agreement with these previous studies, reinforcing the idea that postoperative radiotherapy is not beneficial in patients undergoing sublobar resection.

Lobectomy is generally considered a radical surgery for early-stage NSCLC. Previous studies have evaluated the role of postoperative radiotherapy following lobectomy.[13–17] However, the impact of postoperative radiotherapy in stage pIIIA-N2 NSCLC patients undergoing sublobar resection has not been well studied. By focusing on this patient population, our study addresses

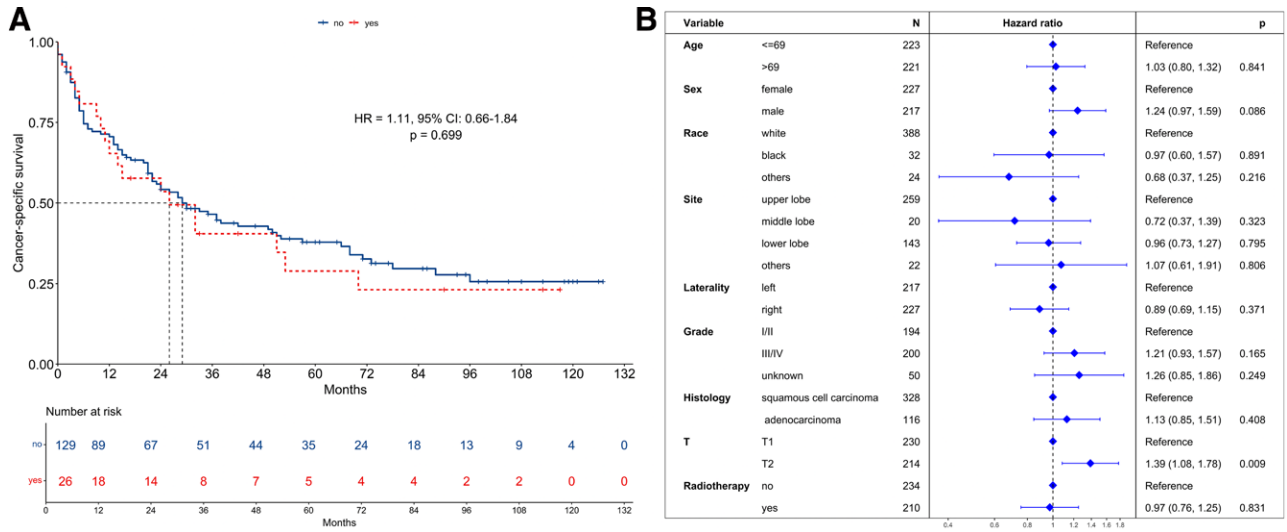

Figure 5. Cancer-specific survival of patients without postoperative chemotherapy. (A) Kaplan–Meier survival curve between postoperative radiotherapy and observation. (B) Multivariable proportional hazards regression analysis of cancer-specific survival.

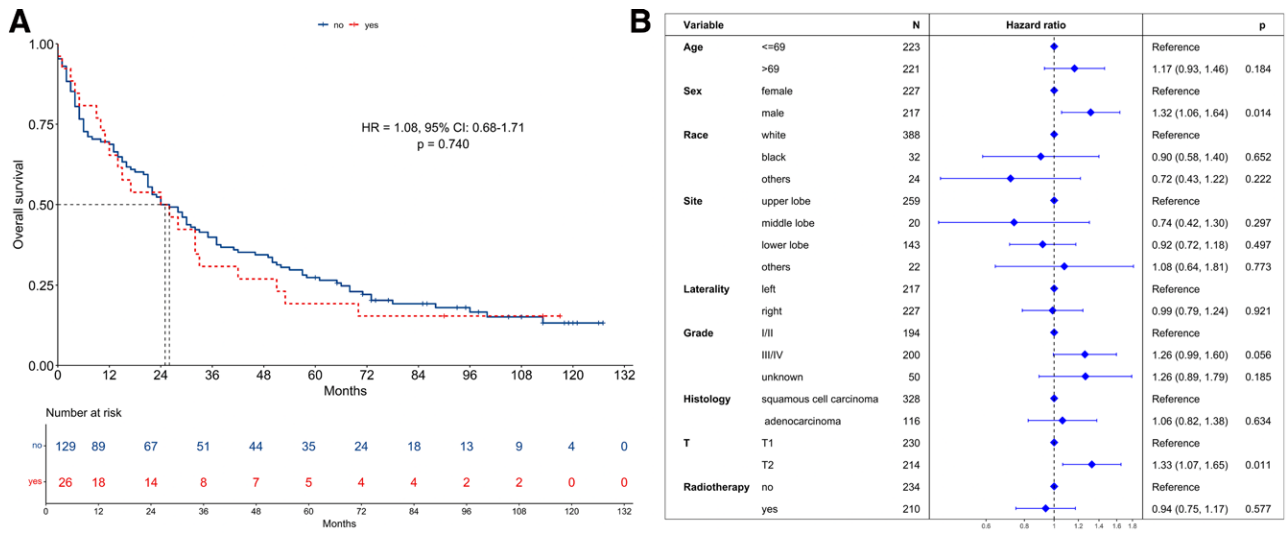

Figure 6. Overall survival of patients without postoperative chemotherapy. (A) Kaplan–Meier survival curve between postoperative radiotherapy and observation. (B) Multivariable proportional hazards regression analysis of overall survival.

an important research gap. Our results suggest that postoperative radiotherapy should be avoided in these patients and underscore the need for further studies to explore effective treatments for this subgroup.

The interpretation of our findings in clinical practice should be approached with caution. Currently, adjuvant therapies such as tyrosine kinase inhibitors are recommended for patients with epidermal growth factor receptor (EGFR) mutations, as these therapies have been shown to improve survival.[24–26] Additionally, adjuvant immunotherapy has been shown to improve outcomes in EGFR wild-type patients.[27,28] However, most patients in our study did not receive adjuvant tyrosine kinase inhibitors or immunotherapy, which may influence treatment outcomes. Future research should further investigate the patterns of treatment failure in these adjuvant therapies, and salvage radiotherapy may be considered for patients with locoregional recurrence. Nevertheless, postoperative adjuvant radiotherapy should not be recommended for these patients.

This study has several strengths. First, by utilizing the SEER database, we were able to include a large cohort of patients, ensuring that the statistical analyses were both reliable and robust. Second, patients were divided into subgroups based on whether they received postoperative chemotherapy, and the similar results in both subgroups further strengthen the validity of our findings. However, there are some limitations. This was a retrospective cohort study based on the SEER database, which may introduce selection bias. Additionally, we could not access detailed information regarding the chemotherapy regimen, cycles, doses, or the radiotherapy techniques used, all of which could influence prognosis. Nevertheless, we employed several analytical methods, including multivariate proportional hazards regression and subgroup analysis, to control for potential confounders. Both analyses provided consistent results, suggesting the reliability of our findings.

In conclusion, our study indicates that postoperative radiotherapy does not improve survival outcomes in patients with stage pIIIA-N2 NSCLC following sublobar resection. The landscape of treatment for this patient population is evolving. Future research focusing on personalized treatment approaches, incorporating new therapies such as immunotherapy and targeted therapy, will be crucial in developing more effective strategies for this challenging subset of NSCLC patients.

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Author contributions

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