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Original Article

World J Oncol. 2024;15(2):309-318

Role of Postoperative Radiotherapy on High-Risk Stage pII-IA-N2 Non-Small Cell Lung Cancer Patients After Complete Resection and Adjuvant Chemotherapy: A Retrospective Cohort Study

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Abstract

Background: The aim of the study was to assess the effectiveness of postoperative radiotherapy in high-risk patients with stage pIIIA-N2 non-small cell lung cancer (NSCLC) following complete resection and adjuvant chemotherapy.

Methods: Data from NSCLC patients within the Surveillance, Epidemiology, and End Results (SEER) database were analyzed. The study examined the association between lymph node ratio (LNR) and both cancer-specific survival (CSS) and overall survival (OS) using restricted cubic spline curves. Patients were categorized into high- and low-risk groups based on established LNR cut-off values, and survival outcomes were compared between those receiving postoperative radiotherapy and those who did not within the high-risk group.

Results: The study included 1,690 patients. An LNR threshold of 0.29 was identified for both CSS and OS. Patients with an LNR ≥ 0.29 demonstrated significantly worse CSS (hazard ratio (HR) = 1.56, 95% confidence interval (CI): 1.37 - 1.78; P < 0.001) and OS (HR = 1.44, 95% CI: 1.28 - 1.62; P < 0.001) compared to those with an LNR < 0.29. In the high-risk group (LNR ≥ 0.29), postoperative radiotherapy did not significantly affect CSS (HR = 0.98, 95% CI: 0.82 - 1.17; P = 0.809) or OS (HR = 0.95, 95% CI: 0.81 - 1.11; P = 0.533).

Conclusions: LNR is a significant prognostic factor in patients with stage pIIIA-N2 NSCLC post complete resection and adjuvant chemotherapy. A higher LNR (≥ 0.29) is associated with poorer CSS and OS. However, postoperative radiotherapy does not confer survival benefits in these high-risk patients. Our findings suggest that postoperative radiotherapy should not be routinely performed in this subgroup. Further research is required to explore effective treatment strategies for these patients.

Keywords: Non-small cell lung cancer; Stage pIIIA-N2; Lymph node ratio; Postoperative radiotherapy

Introduction

Lung cancer remains the leading cause of cancer-related mortality globally, representing approximately 18% of all cancer deaths [1]. Non-small cell lung cancer (NSCLC), which accounts for about 85% of lung cancer cases, is frequently diagnosed at an advanced stage. Notably, a third of patients present with stage III disease [2]. For stage IIIA NSCLC patients, surgery-based multimodal therapies are the cornerstone of treatment [3], with adjuvant chemotherapy demonstrating improvements in both disease-free survival (DFS) and overall survival (OS) in those with completely resected pIIIA-N2 NSCLC [4-6]. However, the role of postoperative radiotherapy in this context is contentious, as reflected by varying findings in the literature [7-10].

Additionally, adjuvant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors have been shown to further enhance DFS in patients with *EGFR* mutations following complete resection and adjuvant chemotherapy [11, 12]. In contrast, adjuvant immunotherapy is recommended for patients with *EGFR* wild-type tumors [13, 14]. While these adjuvant therapies have been associated with improved survival, various factors may influence their efficacy [15-19]. Consequently, the contribution of postoperative radiotherapy in enhancing DFS and OS in this patient population warrants further exploration.

Historically, pIIIA-N2 NSCLC was treated as a homogenous group in research. However, recent studies highlight its heterogeneity [20], which correlates with variable treatment responses [21-26]. This diversity emphasizes the importance of identifying prognostic factors to effectively stratify high-risk patients. Recommendations for postoperative radiotherapy often depend on specific risk factors, such as nodal extracapsular extension, involvement of the highest lymph node station, number of dissected mediastinal lymph node stations, number of positive mediastinal lymph node stations, and surgi-

Manuscript submitted January 30, 2024, accepted February 27, 2024
Published online March 21, 2024

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doi: https://doi.org/10.14740/wjon1832

cal approach [27, 28].

Among these factors, the prognostic significance of examined lymph nodes is an active area of research. Several studies suggest a correlation between the number of examined lymph nodes and patient survival, with higher counts linked to better outcomes [29, 30]. However, the prognostic value of lymph node examination can be influenced by the quality of the surgical procedure [31]. The lymph node ratio (LNR) (the ratio of pathologically metastatic lymph nodes to the total number of harvested lymph nodes) has emerged as a crucial prognostic factor [32-34].

This study aimed to evaluate the impact of LNR on survival outcomes in patients with pIIIA-N2 NSCLC following complete resection and adjuvant chemotherapy. It also seeks to identify high-risk patients based on their LNR and explore the potential role of postoperative radiotherapy in this subset. Our findings are intended to guide clinicians in formulating tailored treatment strategies.

Materials and Methods

Data sources

Our study utilized data from the Surveillance, Epidemiology, and End Results (SEER) program, managed by the National Cancer Institute. As a comprehensive source, SEER offers extensive data on cancer incidence, mortality, and prevalence across the United States. Data extraction was performed using SEER*Stat software (version 8.4.2), focusing on NSCLC cases from 2000 to 2020 to ensure a substantial analytical timeframe.

Study population

The study encompassed patients with histologically confirmed stage pIIIA-N2 squamous cell carcinoma and adenocarcinoma of the lung. Inclusion criteria were limited to patients who underwent radical resection and subsequent adjuvant chemotherapy. We excluded cases involving preoperative radiotherapy, segmentectomy, prior malignancies, neoadjuvant chemotherapy, or indeterminate lymph node status. Comprehensive documentation included demographic factors (age, sex, race), tumor characteristics (primary site, location, grade, histology, T stage), and lymph node status.

Endpoints

The primary endpoint was OS, which was defined as the duration from diagnosis to death from any cause. The secondary endpoint, cancer-specific survival (CSS), was the period from diagnosis to death attributable to NSCLC, as recorded in SEER data.

Stratification of lymph node ratio

In our study, the LNR was defined using the formula: LNR = PLN/TLN, where PLN represents the number of positive lymph nodes, and TLN denotes the total number of harvested lymph nodes. We investigated the prognostic significance of LNR [32-34]. Optimal cut-off values for LNR were established using restricted cubic spline methods [35-37]. This approach allowed us to explore the associations between varying LNR and key survival outcomes (CSS and OS) on a continuous scale. These associations were examined through multivariable Cox regression models, thoughtfully adjusted for a comprehensive set of confounding variables, including age, sex, race, primary site, tumor location, grade, histology, and T stage.

Statistical analysis

Age was categorized based on its median value. We compared categorical factors, including age, sex, race, primary site, tumor location, grade, histology, and T stage, across different LNR groups. These comparisons utilized the χ^2 test or Fisher's exact test, depending on the data distribution.

CSS and OS were compared between the LNR groups using Kaplan-Meier methods, followed by log-rank tests to determine statistical significance in survival differences. Independent prognostic factors impacting CSS and OS were identified using multivariable Cox regression analysis. This analysis adjusted for all the aforementioned categorical factors along with LNR group classification.

Patients were stratified into high-risk and low-risk groups based on CSS and OS outcomes in relation to LNR. High-risk patients were further categorized based on receipt of postoperative radiotherapy. We employed the χ^2 test or Fisher's exact test for comparing categorical factors between the radiotherapy and non-radiotherapy groups. Kaplan-Meier methods with log-rank tests were used to compare CSS and OS between patients who received postoperative radiotherapy and those who did not. A subsequent multivariable Cox regression analysis was conducted, incorporating radiotherapy status as a variable to identify independent prognostic factors.

Statistical analyses were conducted using SPSS Statistics Version 26.0 (IBM Co., Armonk, NY, USA) and R software (version 4.2.2). A two-tailed P value of less than 0.05 was set as the threshold for statistical significance.

Ethics approval and consent to participate

This research has obtained the Institutional Review Board approval. Ethics approval was waived by the Ethics Committee/IRB of Guangxi Medical University Cancer Hospital.

Results

Patient selection

From an initial pool of 1,007,088 lung cancer cases in the SEER database, 1,690 individuals with stage pIIIA-N2 NSCLC met our inclusion criteria. The selection process is depicted in Figure 1.

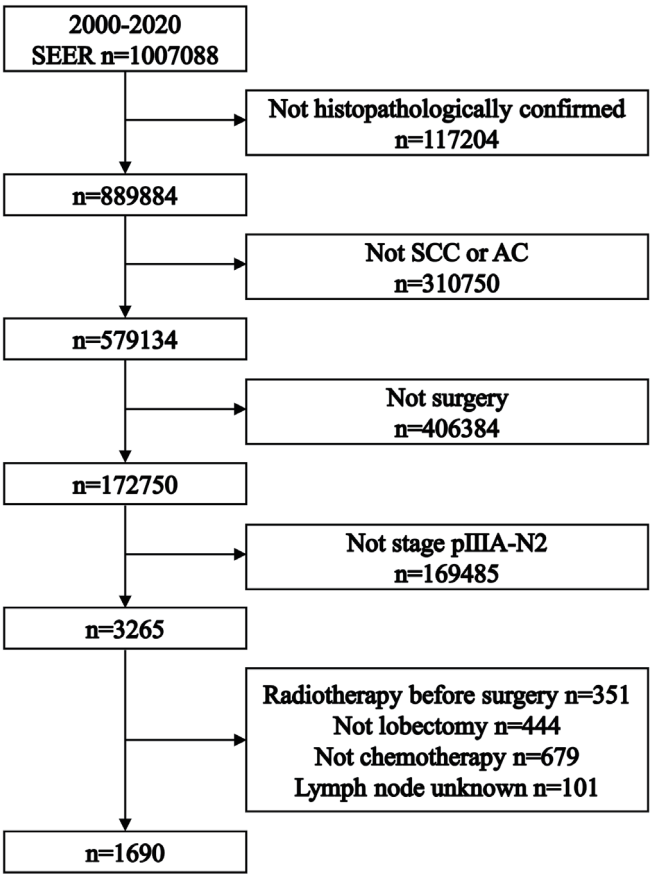

Figure 1. Flowchart illustrating the patient selection process for the study, outlining the criteria for inclusion and exclusion from the Surveillance, Epidemiology, and End Results database. SCC: squamous cell carcinoma. AC: adenocarcinoma.

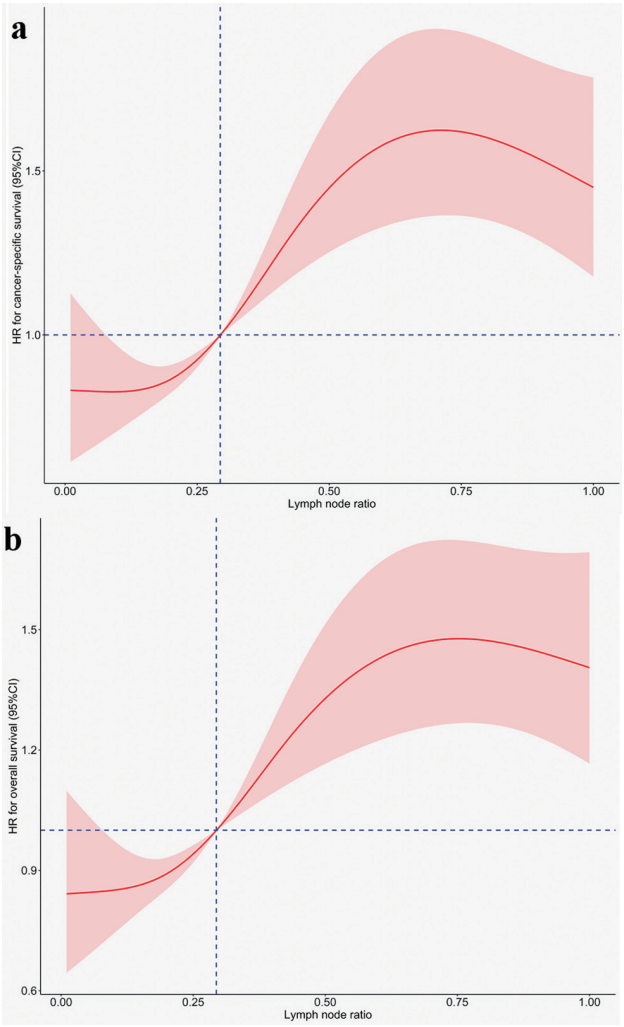

Figure 2. Graphs showing the association between lymph node ratio and survival outcomes, which are analyzed using restricted cubic spline regression models. (a) Cancer-specific survival. (b) Overall survival. HR: hazard ratio; CI: confidence interval.

Association between LNR and survival outcomes

A clear relationship was observed between LNR and survival outcomes using restricted cubic spline regression, adjusted for confounding factors. The multivariable adjusted hazard ratio (aHR) is depicted by a solid red line, with the 95% confidence interval (CI) represented by the red shaded area with four knots. A horizontal solid blue line at an aHR of 1.0 serves as the reference for no association. The vertical solid blue line indicates the cut-off value. An LNR cut-off of 0.29 was identified for both CSS (Fig. 2a) and OS (Fig. 2b). Higher LNRs were linked to poorer CSS and OS.

LNR was categorized into two categories (< 0.29 and ≥ 0.29). Baseline clinical characteristics of the two groups are summarized in Table 1.

Treatment outcomes across LNR groups

Patients with an LNR < 0.29 had a significantly longer median CSS of 93 months, compared to 48 months in the LNR ≥ 0.29 group (Fig. 3a). The 5-year CSS rates were 59.2% for the LNR < 0.29 group and 45.4% for the LNR ≥ 0.29 group. LNR ≥ 0.29 group was associated with decreased CSS (HR = 1.56, 95% CI: 1.37 - 1.78; P < 0.001). LNR ≥ 0.29 was independently prognostic in multivariable analysis (aHR = 1.61, 95% CI: 1.41 - 1.83; P < 0.001) (Fig. 4a).

Similarly, the median OS for patients with an LNR < 0.29 was significantly longer at 66 months, compared to 41 months for the LNR ≥ 0.29 group (Fig. 3b). The 5-year OS rates were 51.8% in the LNR < 0.29 group and 39.1% in the LNR ≥ 0.29 group. The LNR ≥ 0.29 group showed a lower OS (HR = 1.44, 95% CI: 1.28 - 1.62; P < 0.001). LNR ≥ 0.29 was independently prognostic for poorer OS (aHR = 1.49; 95% CI: 1.32 - 1.68; P < 0.001) (Fig. 4b).

Subgroup analysis in LNR ≥ 0.29 group

Patients with an LNR ≥ 0.29 were further divided into postop-

Table 1. Patient Characteristics Between Different Lymph Node Ratio Groups

	LNR < 0.29 (n = 840)	LNR ≥ 0.29 (n = 850)	P
Age			0.440
< 66	418 (49.8%)	406 (47.8%)	
≥ 66	422 (50.2%)	444 (52.2%)	
Sex			0.133
Female	419 (49.9%)	456 (53.6%)	
Male	421 (50.1%)	394 (46.4%)	
Race			0.779
White	696 (82.8%)	695 (81.8%)	
Black	72 (8.6%)	81 (9.5%)	
Others	72 (8.6%)	74 (8.7%)	
Site			0.959
Upper lobe	480 (57.1%)	476 (56.0%)	
Middle lobe	48 (5.7%)	50 (5.9%)	
Lower lobe	287 (34.2%)	300 (35.3%)	
Others	25 (3.0%)	24 (2.8%)	
Laterality			0.650
Left	358 (42.6%)	352 (41.4%)	
Right	482 (57.4%)	498 (58.6%)	
Grade			0.712
I/II	421 (50.1%)	409 (48.1%)	
III/IV	350 (41.7%)	369 (43.4%)	
unknown	69 (8.2%)	72 (8.5%)	
Histology			0.002
Squamous cell carcinoma	625 (74.4%)	687 (80.8%)	
Adenocarcinoma	215 (25.6%)	163 (19.2%)	
T stage			0.783
T1	283 (33.7%)	280 (32.9%)	
T2	557 (66.3%)	570 (67.1%)	

LNR: lymph node ratio.

erative radiotherapy and non-radiotherapy groups, with baseline characteristics detailed in Table 2.

Role of postoperative radiotherapy in LNR ≥ 0.29 group

No significant differences were observed in CSS between the non-radiotherapy and radiotherapy subgroups. CSS was 47 months in the non-radiotherapy group and 49 months in the radiotherapy group. The 5-year CSS rates were 44.5% for the non-radiotherapy group and 46.1% for the radiotherapy group (HR = 0.98; 95% CI: 0.82 - 1.17; P = 0.809) (Fig. 5a). Multivariable Cox regression analysis reaffirmed no significant independent impact of radiotherapy on CSS (aHR = 0.98, 95% CI: 0.82 - 1.17; P = 0.803) (Fig. 6a).

Similarly, OS did not differ significantly between the non-radiotherapy and radiotherapy subgroups. OS was 38 months in the non-radiotherapy group and 41 months in the radiotherapy group. The 5-year OS rates were 37.6% for the non-radiotherapy group and 40.2% for the radiotherapy group (HR = 0.95; 95% CI: 0.81 - 1.11; P = 0.533) (Fig. 5b). Multivariable Cox regression analysis confirmed no significant independent prognostic impact of radiotherapy on OS (aHR = 0.95, 95% CI: 0.81 - 1.11; P = 0.529) (Fig. 6b).

Discussion

This study sought to evaluate the impact of the LNR on treatment outcomes in patients with stage pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy. A pivotal discovery was the establishment of 0.29 as the optimal LNR cutoff for both CSS and OS using sophisticated restricted cubic spline regression models. This threshold effectively delineates

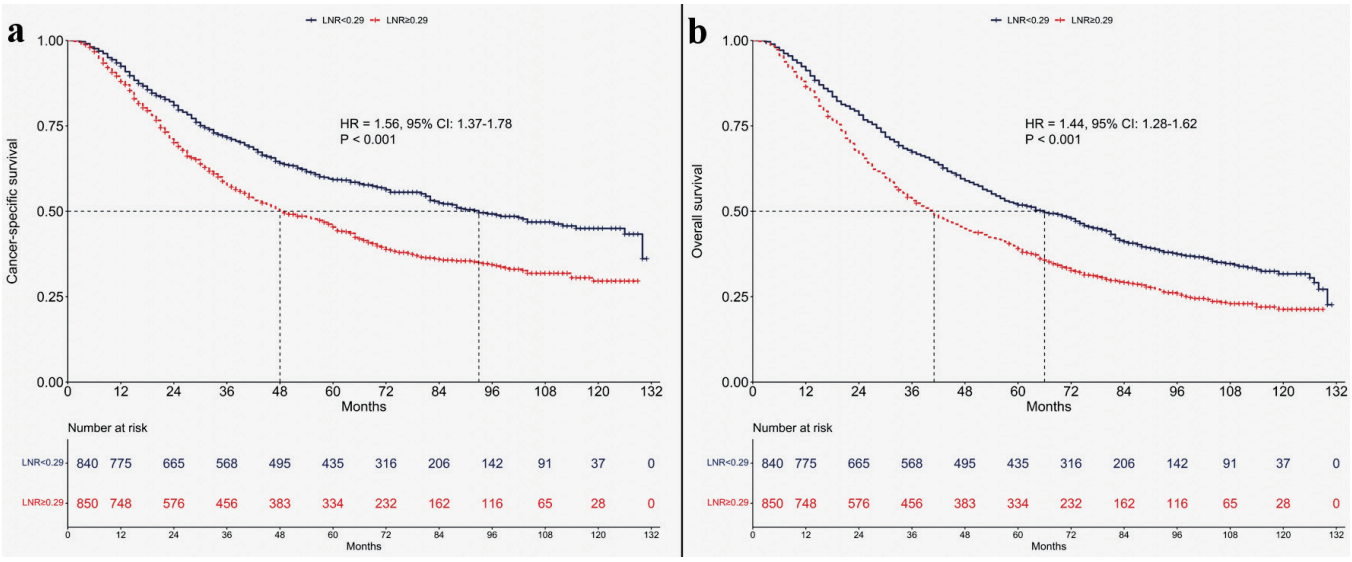

Figure 3. Kaplan-Meier survival curves comparing cancer-specific survival and overall survival between patients categorized by lymph node ratio: those with lymph node ratio < 0.29 versus lymph node ratio ≥ 0.29. (a) Cancer-specific survival. (b) Data on overall survival. LNR: lymph node ratio; HR: hazard ratio; CI: confidence interval.

patients into low-risk (LNR < 0.29) and high-risk (LNR ≥ 0.29) categories. Notably, our analysis revealed that postoperative radiotherapy did not significantly enhance CSS or OS in the high-risk group.

Our findings are in consonance with key trials such as CALGB 9734, PORT-C, and Lung ART, which generally discourage routine postoperative radiotherapy for patients with pIIIA-N2 NSCLC following resection and chemotherapy [7-9]. Despite these guidelines, the continued occurrence of high locoregional recurrence rates, ranging from 20% to 60% [38-40] raises questions about the potential role of postoperative radiotherapy in reducing these recurrences [41-47]. While the PORT-C trial observed a slight improvement in 3-year DFS for patients undergoing postoperative radiotherapy [8], and the Lung ART trial reported extended median DFS [7], these findings suggest that specific patient subgroups might benefit from postoperative radiotherapy.

Although postoperative radiotherapy does improve locoregional recurrence-free survival [7-9], this benefit does not appear to extend to DFS and OS. A possible explanation is that the adverse effects on the lung and heart induced by postoperative radiotherapy may offset its survival benefits. Additionally, salvage treatments (such as local radiotherapy or surgery) following locoregional recurrence could enhance survival in patients who did

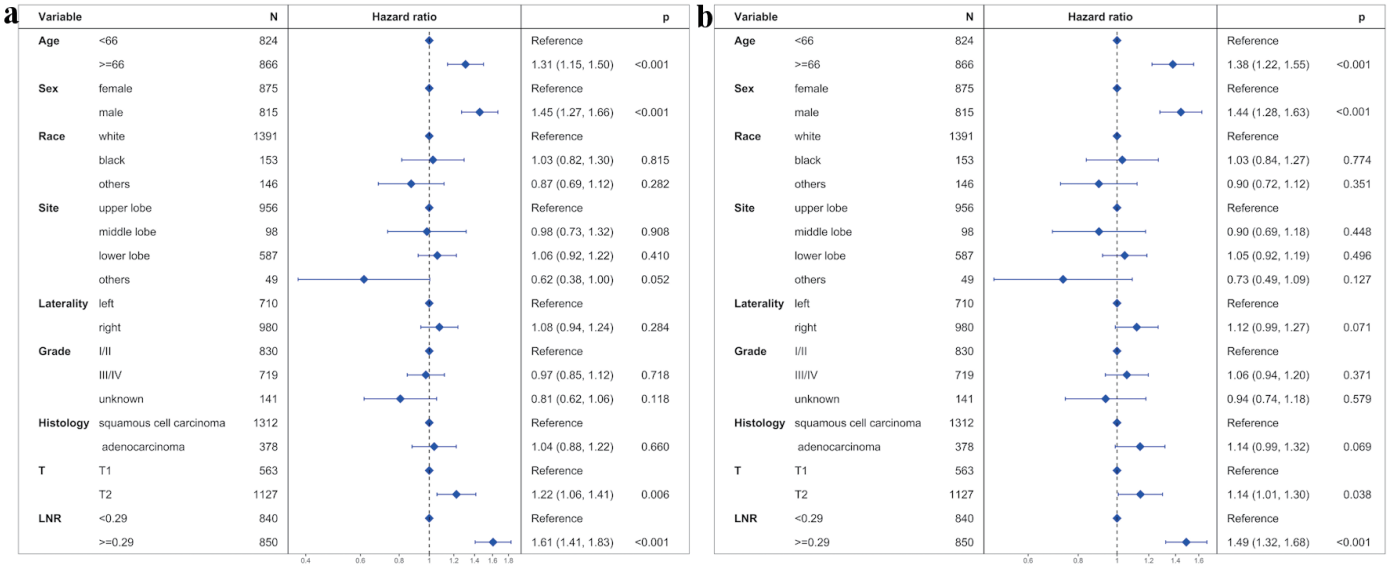

Figure 4. Results of multivariate regression analysis assessing various prognostic factors impacting treatment outcomes. (a) Cancer-specific survival. (b) Overall survival. LNR: lymph node ratio.

Table 2. Patient Characteristics Between Non-Radiotherapy and Radiotherapy Groups in Patients With Lymph Node Ratio ≥ 0.29

	Non-radiotherapy (n = 376)	Radiotherapy (n = 474)	P
Age			0.037
< 66	164 (43.6%)	242 (51.1%)	
≥ 66	212 (56.4%)	232 (48.9%)	
Sex			0.507
Female	207 (55.1%)	249 (52.5%)	
Male	169 (44.9%)	225 (47.5%)	
Race			0.097
White	314 (83.5%)	381 (80.4%)	
Black	38 (10.1%)	43 (9.1%)	
Others	24 (6.4%)	50 (10.5%)	
Site			0.537
Upper lobe	206 (54.8%)	270 (57.0%)	
Middle lobe	23 (6.1%)	27 (5.7%)	
Lower lobe	133 (35.4%)	167 (35.2%)	
Others	14 (3.7%)	10 (2.1%)	
Laterality			0.502
Left	161 (42.8%)	191 (40.3%)	
Right	215 (57.2%)	283 (59.7%)	
Grade			0.635
I/II	178 (47.3%)	231 (48.7%)	
III/IV	169 (44.9%)	200 (42.2%)	
Unknown	29 (7.8%)	43 (9.1%)	
Histology			0.441
Squamous cell carcinoma	299 (79.5%)	388 (81.9%)	
Adenocarcinoma	77 (20.5%)	86 (18.1%)	
T stage			0.350
T1	117 (31.1%)	163 (34.4%)	
T2	259 (68.9%)	311 (65.6%)	

not receive postoperative radiotherapy, leading to comparable OS between postoperative radiotherapy and non-radiotherapy groups.

It is suggested that stage pIIIA-N2 NSCLC patients post complete resection, and adjuvant chemotherapy should receive postoperative radiotherapy based on specific risk prognostic factors [27, 28]. However, the reliance on a single prognostic factor like LNR in determining high-risk patients may be overly simplistic. A more comprehensive approach, integrating multiple factors into an inclusive prognostic model, could provide a more precise identification of patients likely to benefit from postoperative radiotherapy [38, 48].

While our study highlights LNR's significance as a prognostic indicator, its clinical application must be cautiously approached. The evolving landscape of adjuvant therapies, particularly tyrosine kinase inhibitor therapy for *EGFR* mutated cases and immunotherapy for *EGFR* wild-type cases, is crucial [11-14, 49]. Our analysis is constrained by the absence of data on these therapies in the SEER database, underscoring the necessity for further validation in varied clinical contexts.

Future research should initially focus on the patterns of failure post-adjuvant EGFR tyrosine kinase inhibitor therapy and immunotherapy. Subsequent prospective cohort studies comparing treatment outcomes of postoperative radiotherapy and non-radiotherapy in these patients are warranted. Based on these studies, a randomized controlled trial could be conducted to validate the efficacy of postoperative radiotherapy in this specific subgroup.

In conclusion, our study underscores LNR's prognostic value in stage pIIIA-N2 NSCLC patients following complete resection and adjuvant chemotherapy. An LNR threshold of 0.29 is proposed for effective risk stratification. Although patients with higher LNR exhibit poorer CSS and OS, postoperative radiotherapy did not confer survival benefits in this high-risk cohort. Our study suggests refraining from postoperative radiotherapy in these patients and calls for additional research to identify effective treatments for this subgroup.

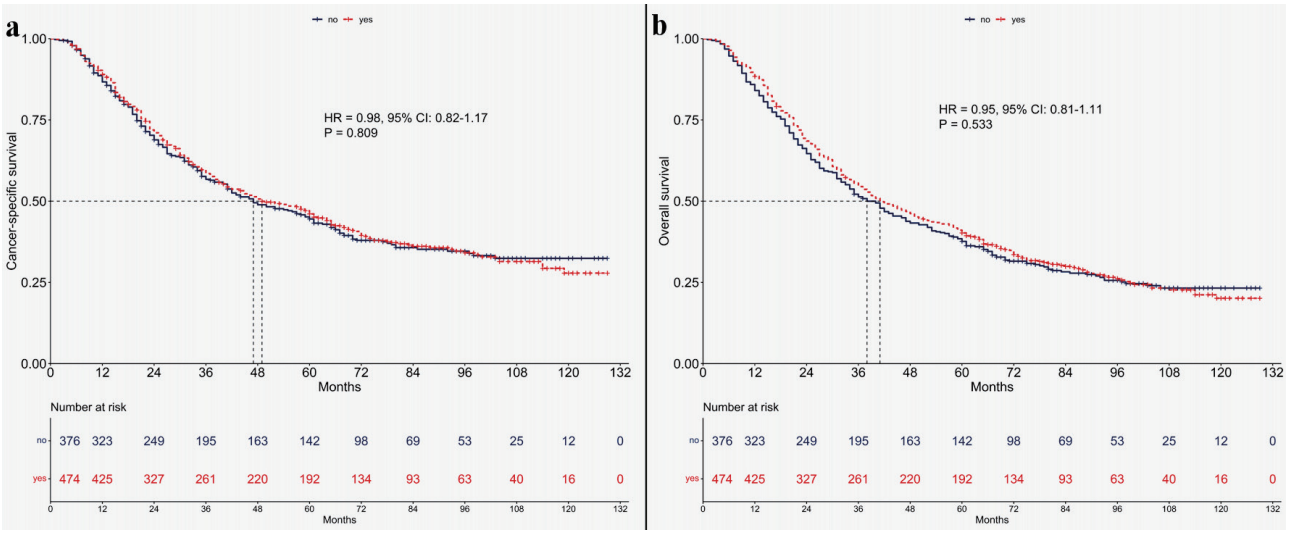

Figure 5. Kaplan-Meier survival curves depicting treatment outcomes between non-radiotherapy and radiotherapy groups in patients with lymph node ratio ≥ 0.29. (a) Cancer-specific survival. (b) Overall survival. HR: hazard ratio; CI: confidence interval.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Informed consent was waived by the Ethics Committee/IRB of Guangxi Medical University Cancer Hospital.

Author Contributions

Conceptualization: Zu Yi Chen. Methodology: Huan Wei Liang and Yang Liu. Formal analysis: Zu Yi Chen and Huan Wei Liang. Investigation: Yang Liu. Resources: Zu Yi Chen and Huan Wei Liang. Validation: Wei Huang. Writing - original draft preparation: Zu Yi Chen. Writing - review and editing: Xin Bin Pan.

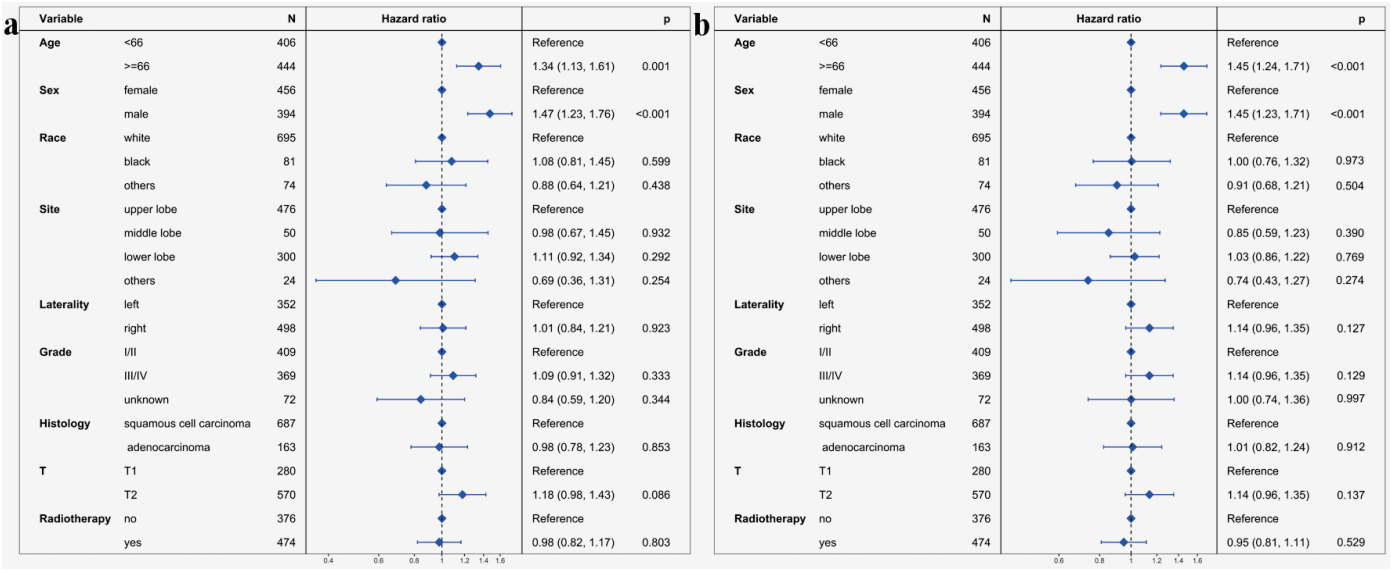

Figure 6. Multivariate regression analysis evaluating various prognostic factors for treatment outcomes in patients with lymph node ratio ≥ 0.29. (a) Cancer-specific survival. (b) Overall survival. LNR: lymph node ratio.

Data Availability

The data are available from the corresponding author upon request.

Abbreviations

NSCLC: non-small cell lung cancer; DFS: disease-free survival; OS: overall survival; EGFR: epidermal growth factor receptor; LNR: lymph node ratio; SEER: the Surveillance, Epidemiology, and End Results; CSS: cancer-specific survival; HR: hazard ratio; CI: confidence interval

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