Original Article

Comparative survival analysis of stage T1-T2N0M0 lung squamous cell carcinoma and adenocarcinoma using SEER data, and nomogram analysis for early-stage lung squamous cell carcinoma

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Background: Lung cancer is one of the most common malignant tumors worldwide. It is of great significance to conduct in-depth research on early lung cancer with a better prognosis. This study aimed to use the Surveillance, Epidemiology, and End Results (SEER) database to compare the clinicopathological characteristics and survival between early squamous cell carcinoma (SQCC) and adenocarcinoma (AC) under the same treatment model, and develop a nomogram for early lung SQCC.

Methods: This study examined 40,325 cases of stage T1-T2N0M0 lung SQCC and AC from 2004 to 2019. Propensity score matching (PSM) was used to reduce bias. Kaplan-Meier curves and Cox proportional hazards models were used for assessing lung cancer-specific survival (LCSS) and overall survival (OS) under various treatments. A nomogram for early-stage SQCC was constructed and validated using the concordance index (C-index), calibration curves, and decision curve analysis (DCA).

Results: In patients with T1-T2N0M0 non-small cell lung cancer (NSCLC), when only radiotherapy was performed, the LCSS of patients in the SQCC group was worse than that of the AC group [hazard ratio (HR) =1.20, 95% confidence interval (CI): 1.079–1.336, P<0.001], and same for 3-year LCSS (55.9% *vs.* 62.7%) and the 5-year LCSS (43.6% *vs.* 47.8%). The OS of patients in the SQCC group was worse than the AC group (HR =1.32, 95% CI: 1.215–1.429, P<0.001). When only surgical treatment was performed, no statistically significant difference was found in the LCSS between the two groups (HR =1.03, 95% CI: 0.965–1.092, P=0.41). The OS of patients in the SQCC group was worse than the AC group (HR =1.25, 95% CI: 1.200–1.309, P<0.001). Additionally, a nomogram was created to predict survival rates for early-stage lung SQCC patients.

Conclusions: The prognosis of patients with T1-T2N0M0 lung SQCC is worse than that of AC patients. Individualized treatment is recommended in the early stages.

Keywords: Early-stage lung adenocarcinoma (early-stage lung AC); early-stage lung squamous cell carcinoma (early-stage lung SQCC); radiotherapy; prognosis; nomogram

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Introduction

In 2020, global cancer statistics reported 2.2 million new lung cancer cases and 1.8 million deaths (1). The World Health Organization (WHO) classifies lung cancer into non-small cell lung cancer (NSCLC) and small cell lung cancer. Among NSCLC, adenocarcinoma (AC) and squamous cell carcinoma (SQCC) are predominant, accounting for 40–50% and 25–30%, respectively (2,3). Early-stage lung cancer is mainly treated with surgery, chemotherapy, and radiation, without multimodal therapy. The prognosis for early-stage AC *vs.* SQCC is debated. Some studies suggest that SQCC has a better prognosis (4,5). A previous study has reported no significant difference in survival between the two pathological types (6), and some studies show that AC has a better prognosis (7,8). Given the insufficient research on the differences in prognosis between the two, it is crucial to analyze clinical and pathological characteristics and prognostic factors. This study uses extensive clinical data for this analysis.

Current cancer treatment protocols and prognosis predictions primarily rely on the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system (9), which focuses on anatomical features, but does not take into account of other factors like age, sex, marital status, race, histology, or treatment modalities (10). Nomograms integrate these factors for a more accurate and intuitive prognosis prediction (10), but few are designed for early-stage lung cancer. To achieve personalized cancer prediction, predictive tools for early-stage lung cancer are essential.

Early screening is improving diagnosis and prognosis, highlighting the need to monitor high-risk groups for recurrence. This study used data from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI) to analyze T1-T2N0M0 early-stage lung SQCC and AC patients, compare survival differences under different treatments, and investigate prognostic factors. The goal was to develop a nomogram for early-stage SQCC to aid intervention strategies. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1602/rc).

Highlight box

Key findings

- When only radiotherapy is given, the lung cancer-specific survival (LCSS) of patients with early-stage lung squamous cell carcinoma is worse than that of patients with adenocarcinoma. However, this difference is not significant when patients are treated with surgery.
- A nomogram of prognosis of early stage lung squamous cell carcinoma is developed.

What is known and what is new?

- Previous studies on radiotherapy for cervical cancer have shown that patients with adenocarcinoma have a worse prognosis than patients with squamous cell carcinoma after radiotherapy.
- This study suggests that patients with early-stage squamous cell lung carcinoma have worse LCSS than patients with adenocarcinoma after radiotherapy. The prognostic response of squamous cell carcinoma and adenocarcinoma histological subtypes to radiotherapy may vary depending on the site of the primary tumor. In addition, this study has constructed a nomogram to predict the survival rate of patients with early-stage squamous cell lung carcinoma to help clinicians evaluate the disease condition and formulate treatment strategies.

What is the implication, and what should change now?

- When formulating radiotherapy plans, radiation oncologists should pay attention to the following issues: When patients with early lung cancer receive radiotherapy, it may be not perfect to share a fixed radiotherapy plan for squamous cell carcinoma and adenocarcinoma. In the era of personalized medicine, even when formulating treatment strategies for early-stage lung cancer patients, pathological differences should be considered separately for analysis, aiming to provide more accurate treatment in the future.

Methods

Study population

The SEER database is a large-scale cancer registry in North America, covering approximately 48.0% of the U.S. population, with data on cancer survival and mortality (11). This study used SEER*Stat software version 8.4.2 (https://seer.cancer.gov/seerstat/) to download cases from the Incidence-SEER Research Plus data, 18 Registries, Nov 2020 Sub [2000–2018].

Inclusion criteria were: (I) single primary lung cancer diagnosed between 2004 and 2019; (II) clear follow-up times, survival status, and cause of death. Initially, 530,380 patients were screened. Exclusion criteria were: (I) lesions diameter >5 cm; (II) unknown tumor location, surgical status, grade, race, marital status, or laterality; (III) non-squamous or non-AC pathology per the International Classification of Diseases for Oncology-3rd Edition (ICD-O-3); (IV) lymph node or distant metastasis; (V) Tis (stage 0) disease. This resulted in 12,071 SQCC patients

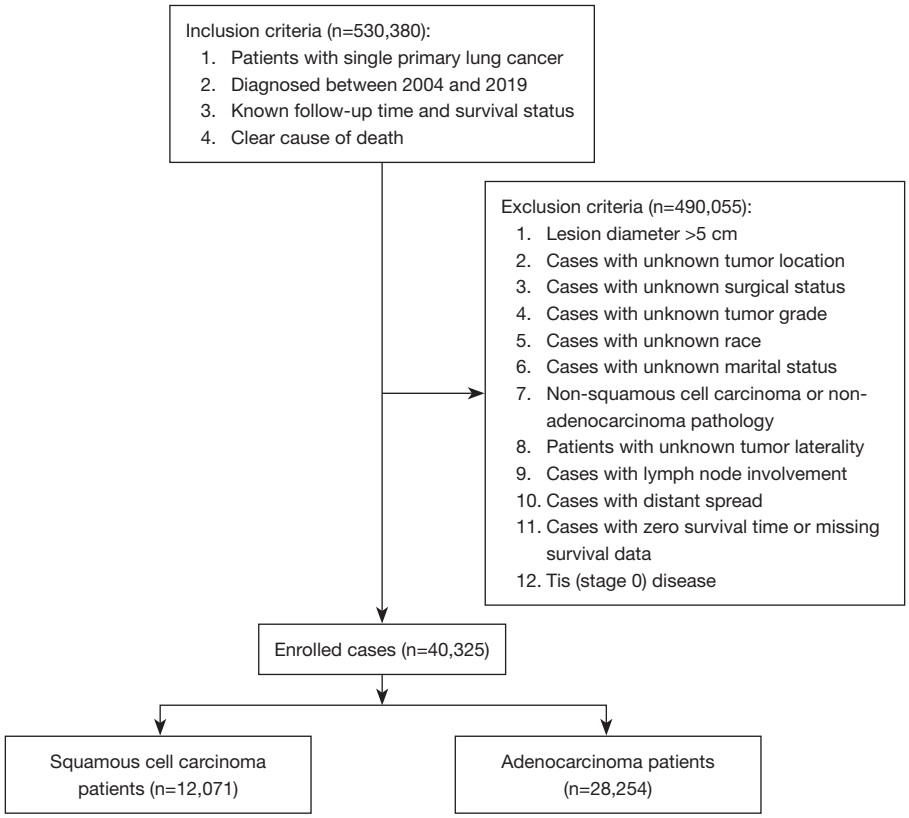

Figure 1 Data screening flow chart.

and 28,254 AC patients, totaling 40,325. The screening process is shown in *Figure 1*.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As the SEER database is public and does not contain sensitive personal information, informed consent and institutional review board approval were not required.

Demographic and clinical variables

The analysis included variables: demographic characteristics (gender, age, race, marital status), disease characteristics (pathological type, tumor laterality, location, grade, size), treatment information (surgery, chemotherapy, radiotherapy), survival time, and status. Patients had tumor diameters ≤5 cm and were classified as stage IA-IIA lung SQCC and AC per the 8th edition AJCC criteria for T1-T2N0M0. Events of interest were overall survival (OS) and lung cancer-specific survival (LCSS). OS is the time from lung cancer diagnosis to death from any cause or last follow-up. LCSS is the time from diagnosis to death specifically from lung cancer.

Statistical analysis

Clinical and pathological characteristics of early-stage lung AC and SQCC were compared using categorical variables represented by frequency and proportion, analyzed with the Chi-squared test. Survival analysis was conducted using Kaplan-Meier method to plot OS and LCSS curves, estimating median OS. Propensity score matching (PSM) at a 1:1 ratio eliminated differences in baseline characteristics, followed by log-rank testing to assess survival differences. Multivariable analysis on OS factors in early-stage lung SQCC used the Cox proportional hazards model to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical significance was defined as $P<0.05$.

Nomograms predicting 1-, 3-, and 5-year survival rates for early-stage lung SQCC were constructed based on independent prognostic factors. Predictive ability and accuracy of nomograms were evaluated by discrimination (concordance index, C-index) and calibration (calibration

curves) (12,13). Clinical utility was assessed using decision curve analysis (DCA) (14). A risk classification system was developed from the total scores to identify high and low prognostic groups. All analyses were conducted using R (version 4.3.2, https://www.rproject.org/).

Results

Clinical characteristics

This study included 12,071 patients with SQCC and 28,254 with AC. Chi-squared tests showed significant differences in demographics, disease features, and treatment modalities between the groups (*Table 1*). Patients under 60 were more prevalent in the AC group (19.9% *vs.* 10.5%, P<0.001), while those over 70 were more common in the SQCC group (57.6% *vs.* 46.3%, P<0.001). The AC group had 40.1% males and 59.9% females (P<0.001), compared to 56.4% males and 43.6% females in the SQCC group (P<0.001). Marital status showed both groups predominantly married (57.2% *vs.* 53.4%, P<0.001), with a higher proportion of widowed/divorced in the SQCC group (34.1% *vs.* 29.3%). Both cancers were more common on the right side (60.2% *vs.* 56.5%, P<0.001). About 60% of tumors were in the upper lobes for both types, followed by lower and middle lobes, with the main bronchus being least common. SQCC was more frequent in the main bronchus (1.2% *vs.* 0.1%, P<0.001). Histological grade showed AC cells better differentiated (26.9% *vs.* 3.5%, P<0.001). More SQCC patients received radiotherapy (19.3% *vs.* 8.8%, P<0.001) and fewer underwent surgery (77.3% *vs.* 89.5%, P<0.001).

Survival differences between lung AC and lung SQCC

Patients with stage T1-T2N0M0 NSCLC were categorized into four treatment groups: surgery-only (31,604 patients), radiotherapy-only (3,371 patients), chemotherapy-only (205 patients), and untreated (1,515 patients). Significant demographic differences were adjusted using PSM, considering age, race, gender, marital status, tumor laterality, tumor location, histological grade, and tumor size. Kaplan-Meier survival analysis was performed on the matched groups.

Comparison of survival prognosis in patients receiving only chemotherapy

The HR for LCSS in the chemotherapy-only group compared to the untreated group was 0.88 (95% CI: 0.670–1.114, P=0.28) (*Figure 2A*), and the HR for OS in the chemotherapy-only group was 0.82 (95% CI: 0.663–1.010, P=0.053) (*Figure 2B*), indicating no statistical difference.

Comparison of survival prognosis in patients receiving only radiotherapy

The HR for LCSS in the radiotherapy-only group compared to the untreated group was 0.38 (95% CI: 0.342–0.420, P<0.001) (*Figure 3A*), indicating that the risk of lung cancer-specific death in the radiotherapy-only group is 0.38 times that of the untreated group. The HR for OS in the radiotherapy-only group was 0.54 (95% CI: 0.500–0.590, P<0.001) (*Figure 3B*), showing that the risk of death in the radiotherapy-only group is 0.54 times that of the untreated group.

When treated with radiotherapy alone, patients with SQCC had worse LCSS compared to those with AC (HR =1.20, 95% CI: 1.079–1.336, P<0.001) (*Figure 3C*). AC patients had better 3-year LCSS (62.7% *vs.* 55.9%) and better 5-year LCSS (47.8% *vs.* 43.6%). For OS, SQCC patients also had worse outcomes compared to AC patients (HR =1.32, 95% CI: 1.215–1.429, P<0.001) (*Figure 3D*). The median OS was 35 months (95% CI: 32–37) for AC patients and 27 months (95% CI: 25–28) for SQCC patients. AC patients had better 3-year OS (48.0% *vs.* 37.6%) and better 5-year OS (29.7% *vs.* 20.6%).

Comparison of survival prognosis in patients undergoing surgery alone

In the surgery-alone group, the HR for LCSS compared to the untreated group was 0.08 (95% CI: 0.069–0.088, P<0.001) (*Figure 4A*). For OS, the HR was 0.09 (95% CI: 0.085–0.104, P<0.001) (*Figure 4B*).

Under surgery alone, the HR for LCSS comparing SQCC to AC was 1.03 (95% CI: 0.965–1.092, P=0.41) (*Figure 4C*), indicating no significant difference. AC patients had better 3-year LCSS (83.1% *vs.* 81.7%) but slightly worse 5-year LCSS (73.9% *vs.* 74.4%). For OS, SQCC patients had worse outcomes (HR =1.25, 95% CI: 1.200–1.309, P<0.001) (*Figure 4D*). Median OS was 88 months (95% CI: 85–91) for AC and 72 months (95% CI: 69–74) for SQCC. AC patients had better 3-year OS (75.0% *vs.* 69.8%) and 5-year OS (61.3% *vs.* 55.9%).

After PSM, survival analysis showed that for T1-T2N0M0 stage SQCC and AC patients, both radiotherapy and surgery improved LCSS and OS. Chemotherapy alone

Table 1 Comparison of clinicopathological characteristics of lung squamous cell carcinoma and lung adenocarcinoma

Variables	Overall (N=40,325)	Adenocarcinoma (N=28,254)	Squamous cell carcinoma (N=12,071)	P
Age (years)				<0.001
<60	6,898 (17.1)	5,635 (19.9)	1,263 (10.5)	
60–69	13,379 (33.2)	9,523 (33.7)	3,856 (31.9)	
70–79	14,371 (35.6)	9,366 (33.1)	5,005 (41.5)	
≥80	5,677 (14.1)	3,730 (13.2)	1,947 (16.1)	
Sex				<0.001
Female	22,194 (55.0)	16,933 (59.9)	5,261 (43.6)	
Male	18,131 (45.0)	11,321 (40.1)	6,810 (56.4)	
Race				<0.001
White	33,672 (83.5)	23,072 (81.7)	10,600 (87.8)	
Black	3,220 (8.0)	2,299 (8.1)	921 (7.6)	
Others	3,433 (8.5)	2,883 (10.2)	550 (4.6)	
Marital status				<0.001
Married	22,602 (56.0)	16,157 (57.2)	6,445 (53.4)	
Widowed/divorced	12,392 (30.7)	8,271 (29.3)	4,121 (34.1)	
Others	5,331 (13.2)	3,826 (13.5)	1,505 (12.5)	
Laterality				<0.001
Left	16,480 (40.9)	11,231 (39.8)	5,249 (43.5)	
Right	23,845 (59.1)	17,023 (60.2)	6,822 (56.5)	
Primary site				<0.001
Upper lobe	24,906 (61.8)	17,544 (62.1)	7,362 (61.0)	
Middle lobe	2,064 (5.1)	1,523 (5.4)	541 (4.5)	
Lower lobe	13,181 (32.7)	9,155 (32.4)	4,026 (33.4)	
Main bronchus	174 (0.4)	32 (0.1)	142 (1.2)	
Tumor size (cm)				<0.001
≤1.0	2,933 (7.3)	2,302 (8.1)	631 (5.2)	
1.1–2.0	15,211 (37.7)	11,517 (40.8)	3,694 (30.6)	
2.1–3.0	12,168 (30.2)	8,585 (30.4)	3,583 (29.7)	
3.1–4.0	6,640 (16.5)	4,069 (14.4)	2,571 (21.3)	
4.1–5.0	3,373 (8.4)	1,781 (6.3)	1,592 (13.2)	
Grade				<0.001
Grade I	8,025 (19.9)	7,598 (26.9)	427 (3.5)	
Grade II	20,022 (49.7)	13,973 (49.5)	6,049 (50.1)	
Grade III	12,054 (29.9)	6,545 (23.2)	5,509 (45.6)	
Grade IV	224 (0.6)	138 (0.5)	86 (0.7)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Overall (N=40,325)	Adenocarcinoma (N=28,254)	Squamous cell carcinoma (N=12,071)	P
Surgery				<0.001
No	5,695 (14.1)	2,958 (10.5)	2,737 (22.7)	
Yes	34,630 (85.9)	25,296 (89.5)	9,334 (77.3)	
Radiation				<0.001
No	35,509 (88.1)	25,762 (91.2)	9,747 (80.7)	
Yes	4,816 (11.9)	2,492 (8.8)	2,324 (19.3)	
Chemotherapy				<0.001
No	36,985 (91.7)	26,071 (92.3)	10,914 (90.4)	
Yes	3,340 (8.3)	2,183 (7.7)	1,157 (9.6)	

Data are presented as n (%).

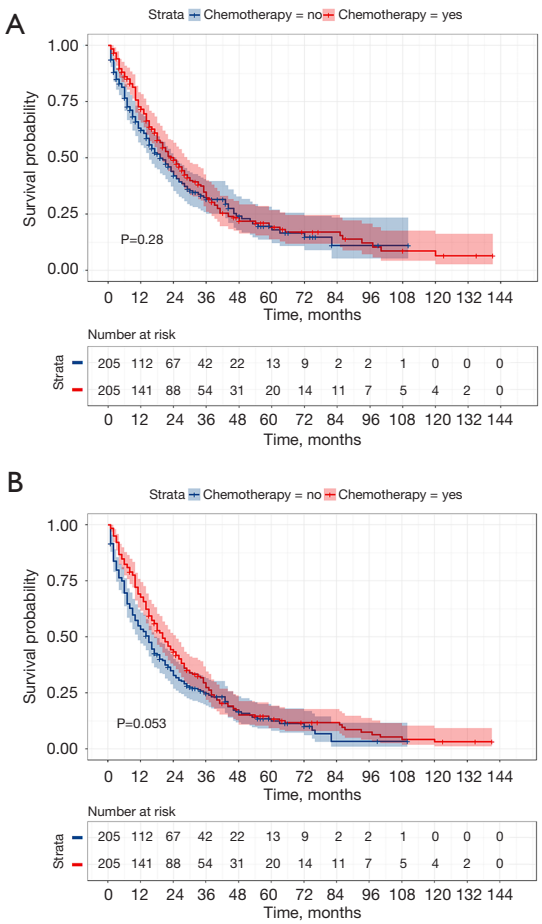

Figure 2 Difference in survival between T1-T2N0M0 non-small cell lung cancer patients receiving chemotherapy and those not receiving chemotherapy after PSM. (A) LCSS. (B) OS. LCSS, lung cancer specific survival; OS, overall survival; PSM, propensity score matching.

showed no significant differences in LCSS and OS. Among surgery or radiotherapy-treated patients, those with SQCC had poorer OS compared to AC. For LCSS, SQCC patients receiving radiotherapy alone had worse outcomes than those with AC. However, among surgery-treated patients, there was no significant difference between the two groups.

Single and multifactorial analysis of early SQCC prognosis

The Cox proportional hazards model was used for single-factor analysis of all known variables, as detailed in *Table 2*. Factors that were statistically significant in this analysis were then included in a multifactor analysis. This revealed that age, gender, race, marital status, tumor location, tumor size, radiotherapy, and surgery are independent prognostic factors for OS in early-stage squamous cell lung cancer patients (*Table 2*). Age ≥60 (HR >1, P<0.001), male gender (HR =1.244, P<0.001), divorced or widowed marital status (HR =1.162, P<0.001), tumors located in the main bronchus (HR =1.28, P=0.01), and larger tumor size (HR >1, P<0.001) were identified as risk factors negatively impacting survival. Conversely, undergoing surgery (HR =0.294, P<0.001) or radiotherapy (HR =0.706, P<0.001) were found to be protective factors that improve survival. The P value for chemotherapy alone was 0.40, indicating no statistically significant difference (P>0.05).

Construction of nomogram and risk classification system

Using the independent factors identified, we developed

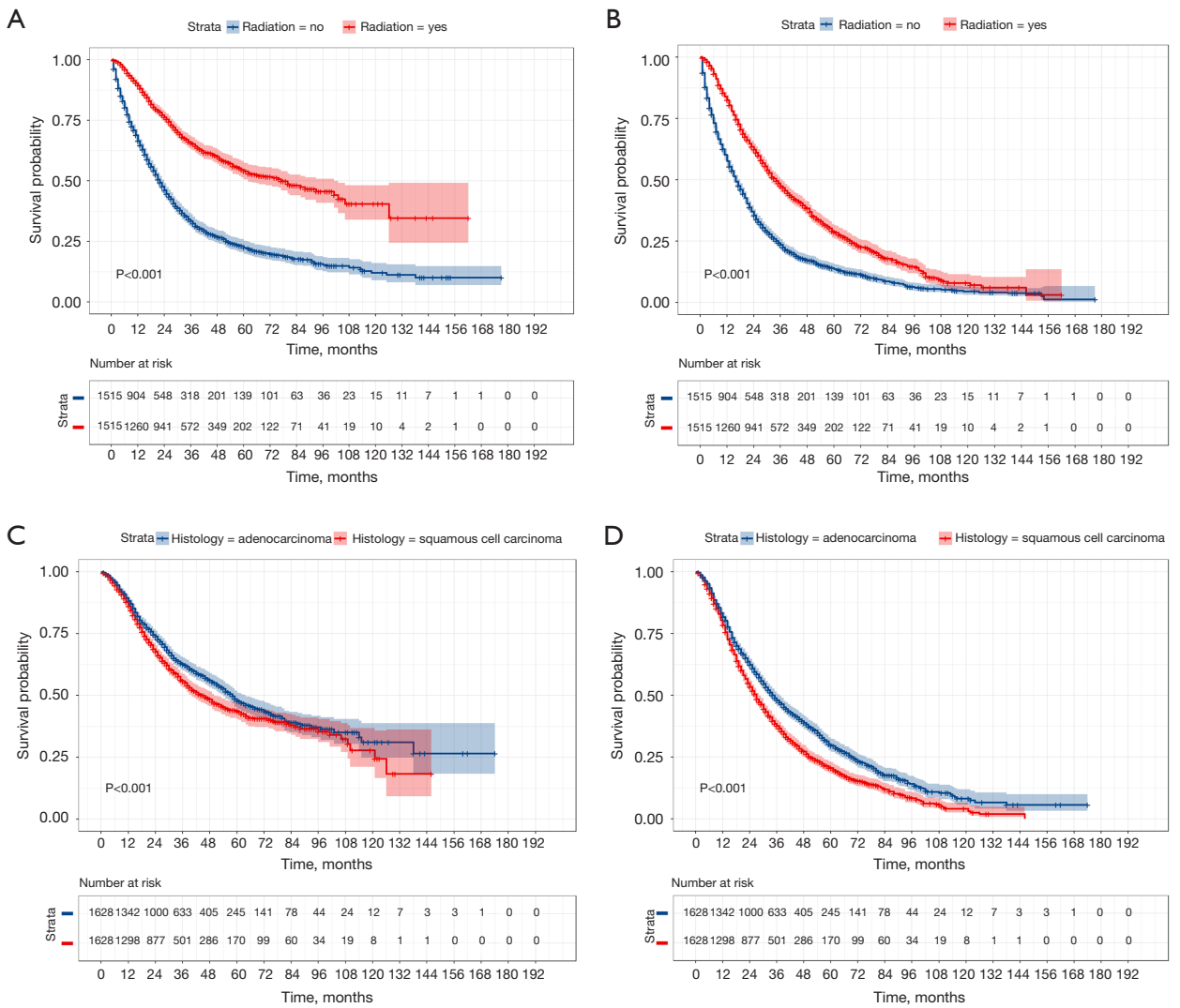

Figure 3 Difference in survival in patients receiving radiotherapy alone. (A,B) Difference in survival between T1-T2N0M0 non-small cell lung cancer patients receiving radiotherapy and those not receiving radiotherapy after PSM. (A) LCSS; (B) OS. (C,D) Difference in survival between patients with lung squamous cell carcinoma and adenocarcinoma after PSM. (C) LCSS; (D) OS. LCSS, lung cancer specific survival; OS, overall survival; PSM, propensity score matching.

a nomogram to predict 1-, 3-, and 5-year survival rates for early-stage squamous cell lung cancer patients. We enrolled 12,071 patients with tumors ≤5 cm in diameter, dividing them into a training set (n=8,449) and a validation set (n=3,622) at a 7:3 ratio, ensuring comparable baseline characteristics (*Table 3*). The nomogram, shown in *Figure 5*, was validated with the concordance index (C-index), calibration plots, and DCA. The C-index was 0.662 for the training set and 0.647 for the validation set, indicating good predictive accuracy. The calibration plots (*Figure 6A-6F*) demonstrated strong agreement between predicted and actual 1-, 3-, and 5-year OS probabilities. Additionally, the DCA plots (*Figure 7A-7F*) showed a significant net benefit across nearly all threshold probabilities for the 1-, 3-, and 5-year predictions.

The nomogram model allows for rapid prognosis prediction using clinical data (age, sex, race, marital status, tumor location, histologic grade, tumor size, surgery, and radiotherapy) for each patient. Finally, we established an OS risk classification system, stratifying patients into high and low-risk groups with cutoff values of 141.35 in the training set and 141.06 in the validation set. The low-

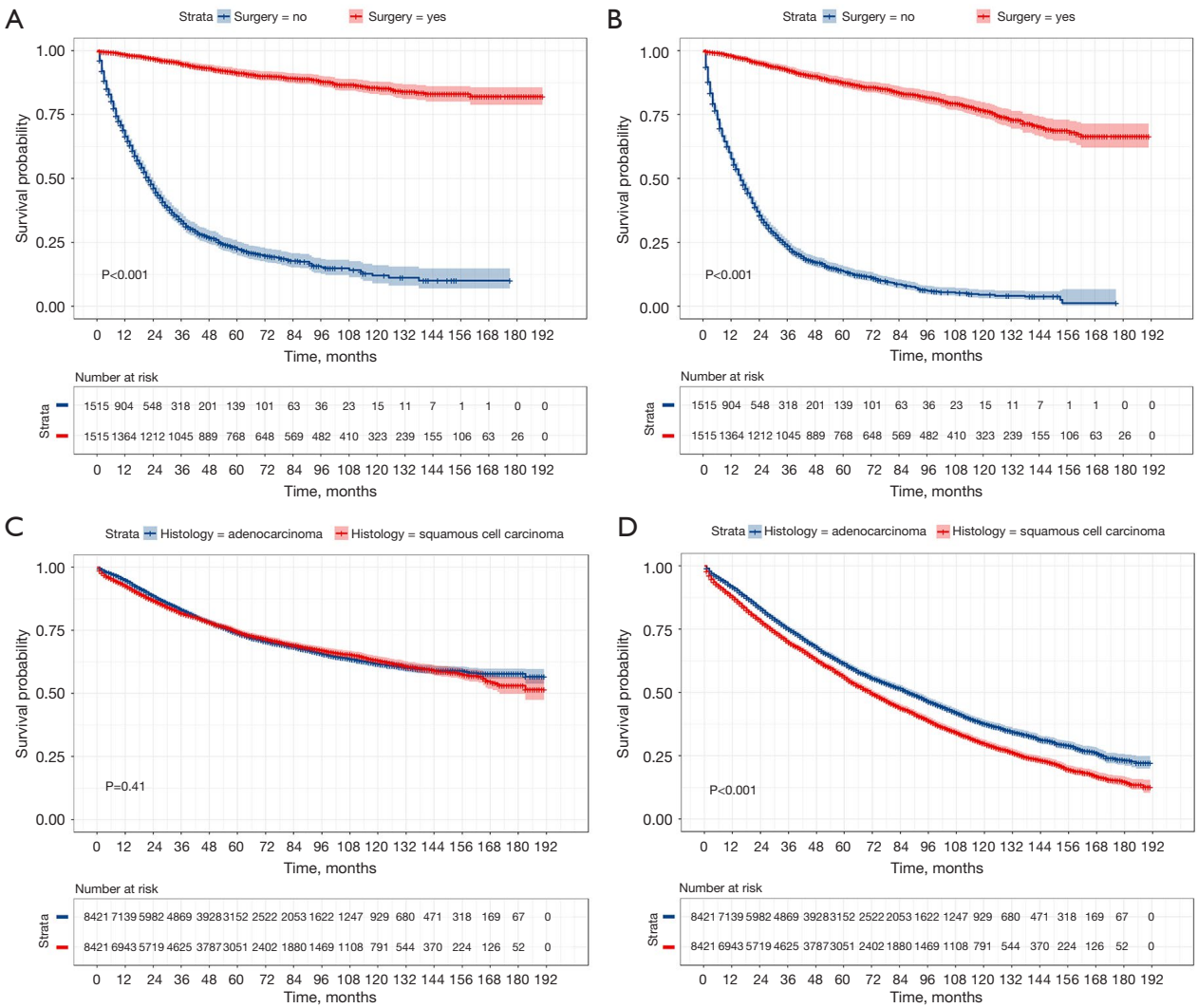

Figure 4 Difference in survival in patients receiving surgery. (A,B) Difference in survival between T1-T2N0M0 non-small cell lung cancer patients receiving surgery and those not receiving surgery after PSM. (A) LCSS; (B) OS. (C,D) Difference in survival between patients with lung squamous cell carcinoma and adenocarcinoma after PSM. (C) LCSS; (D) OS. LCSS, lung cancer specific survival; OS, overall survival; PSM, propensity score matching.

risk group exhibited significant survival benefits (P<0.001, *Figure 8A,8B*).

Discussion

Some studies suggest that treating lung AC and SQCC as separate clinical entities and adopting personalized management and treatment strategies are increasingly preferable in the future (15-17). Our study identified differences in clinical and pathological characteristics, as well as prognosis, between early-stage lung SQCC and AC patients. Irrespective of being treated with surgery or radiation therapy, patients with early-stage lung SQCC had a poorer prognosis. We analyzed factors affecting SQCC prognosis and created survival curves based on the data. The strength of our study lies in its large population data, sufficient follow-up duration, matched analysis of differences among early-stage lung cancer patients, and exploration of prognosis differences under a single treatment modality, adhering to a first principles approach. This comprehensive analysis is relatively rare. With the global increase in cancer incidence, early implementation

Table 2 Univariate and multivariate Cox regression analysis of OS in patients with early lung squamous cell carcinoma

Characteristics	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
<60	Reference			Reference		
60–69	1.45	1.319–1.595	<0.001	1.421	1.291–1.563	<0.001
70–79	2.004	1.829–2.196	<0.001	1.888	1.72–2.073	<0.001
≥80	3.135	2.84–3.461	<0.001	2.376	2.142–2.634	<0.001
Sex						
Female	Reference			Reference		
Male	1.159	1.106–1.215	<0.001	1.244	1.183–1.308	<0.001
Race						
White	Reference			Reference		
Black	0.985	0.902–1.0756	0.74	0.928	0.849–1.015	0.10
Others	0.8701	0.7755–0.9762	0.02	0.831	0.74–0.933	0.002
Marital status						
Married	Reference			Reference		
Widowed/divorced	1.235	1.1747–1.298	<0.001	1.162	1.101–1.226	<0.001
Others	1.022	0.9477–1.102	0.57	1.068	0.989–1.154	0.09
Laterality						
Left	Reference			–		
Right	1.007	0.9615–1.055	0.76	–	–	–
Primary site						
Upper lobe	Reference			Reference		
Middle lobe	0.9929	0.8861–1.112	0.90	0.986	0.88–1.105	0.81
Lower lobe	1.0787	1.0266–1.134	0.003	1.033	0.983–1.086	0.20
Main bronchus	1.6102	1.3314–1.948	<0.001	1.28	1.054–1.554	0.01
Tumor size (cm)						
≤1.0	Reference			Reference		
1.1–2.0	1.058	0.9393–1.193	0.35	0.959	0.851–1.081	0.49
2.1–3.0	1.387	1.2325–1.561	<0.001	1.174	1.042–1.322	0.008
3.1–4.0	1.594	1.4133–1.797	<0.001	1.352	1.198–1.526	<0.001
4.1–5.0	1.659	1.4634–1.881	<0.001	1.372	1.209–1.558	<0.001
Grade						
Grade I	Reference			–		
Grade II	0.9585	0.8438–1.089	0.51	–	–	–
Grade III	0.9869	0.8687–1.121	0.84	–	–	–
Grade IV	1.2013	0.9084–1.589	0.20	–	–	–

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Surgery						
No	Reference			Reference		
Yes	0.3315	0.3147–0.3493	<0.001	0.294	0.27–0.32	<0.001
Radiation						
No	Reference			Reference		
Yes	2.132	2.019–2.252	<0.001	0.706	0.647–0.77	<0.001
Chemotherapy						
No	Reference			Reference		
Yes	1.094	1.014–1.18	0.02	0.966	0.891–1.047	0.40

OS, overall survival; HR, hazard ratio; CI, confidence interval.

and dissemination of diagnostic methods are crucial. Through this population-based research, we aim to enhance the understanding of the heterogeneity between early-stage lung SQCC and AC. Given the poorer prognosis of early-stage SQCC compared to AC, there should be increased post-diagnosis attention and consideration for personalized management strategies for these high-risk groups.

Clinical and pathological characteristics

Our study reveals that both lung AC and SQCC are more frequently found in the right lung, primarily affecting the upper and lower lobes. SQCC tends to occur slightly more in the main bronchus compared to AC. Consistent with previous reports, SQCC is more likely to occur in the central region, whereas AC is more common in the peripheral region (18,19). We also found that SQCC tends to have poorer differentiation (grades III–IV, 46.3% *vs.* 23.7%, P<0.001), occurs at an older age, and has a higher proportion of male patients. These findings align with earlier research (20,21).

Prognostic differences in patients with stage T1-T2N0M0 lung SQCC and AC

This study first adjusted for intergroup differences before analyzing the prognosis of stage T1-T2N0M0 SQCC and AC under various treatments. The findings suggest that surgery or radiation therapy can improve LCSS and OS. However, the impact of chemotherapy alone on LCSS and OS was not statistically significant. To our knowledge, this is one of the few large-scale comparative analyses of prognosis following different treatments for early-stage lung SQCC and AC, providing robust evidence supporting the poorer prognosis associated with SQCC histology.

For early-stage NSCLC, surgery is generally the preferred treatment (22,23), with 5-year OS rates ranging from 50% to 80% (2). Some postoperative studies suggest a better prognosis for SQCC. For example, Pfannschmidt *et al.* analyzed 2,083 postoperative lung cancer patients (stages I–IV) and found significantly better 5-year survival rates for SQCC compared to AC (P=0.008) (4). Similarly, Strand *et al.* included 3,211 postoperative lung cancer patients (stages I–IV) and reported through Cox regression analysis that AC had a worse prognosis than SQCC across all patients (5). Additionally, a multifactorial analysis of IA stage lung cancer patients post-surgery showed no significant correlation between histological type and OS (P=0.38) or disease-specific survival (P=0.39) (6). Conversely, other studies support a better prognosis for AC. For instance, a retrospective study by Izaki *et al.* (7) analyzed the prognosis of 628 patients with stage I–IIA lung cancer after surgery in Japan. The 5-year OS rate was 90% in patients with AC and 77% in patients with SQCC (P<0.01), confirming that patients with lung AC had better survival outcomes than those with lung SQCC. Maeda *et al.* reported statistically significant differences in OS between stage I–II lung AC and SQCC post-surgery, with 5-year survival rates of 79.7% and 63.8%, respectively (24). Similarly, JL Lopez Guerra *et al.* found a significantly increased risk of death

Table 3 Baseline characteristics of patients with early lung squamous cell carcinoma of the nomogram in the training set and validation set

Variables	Training set (N=8,449)	Validation set (N=3,622)
Age (years)		
<60	896 (10.6)	367 (10.1)
60–69	2,703 (32.0)	1,153 (31.8)
70–79	3,492 (41.3)	1,513 (41.8)
≥80	1,358 (16.1)	589 (16.3)
Sex		
Female	3,664 (43.4)	1,597 (44.1)
Male	4,785 (56.6)	2,025 (55.9)
Race		
White	7,397 (87.5)	3,203 (88.4)
Black	652 (7.7)	269 (7.4)
Others	400 (4.7)	150 (4.1)
Marital status		
Married	4,495 (53.2)	1,950 (53.8)
Widowed/divorced	2,895 (34.3)	1,226 (33.8)
Others	1,059 (12.5)	446 (12.3)
Laterality		
Left	3,647 (43.2)	1,602 (44.2)
Right	4,802 (56.8)	2,020 (55.8)
Primary site		
Upper lobe	5,132 (60.7)	2,230 (61.6)
Middle lobe	383 (4.5)	158 (4.4)
Lower lobe	2,824 (33.4)	1,202 (33.2)
Main bronchus	110 (1.3)	32 (0.9)
Tumor size (cm)		
≤1	438 (5.2)	193 (5.3)
1.1–2	2,618 (31.0)	1,076 (29.7)
2.1–3	2,495 (29.5)	1088 (30.0)
3.1–4	1,763 (20.9)	808 (22.3)
4.1–5	1,135 (13.4)	457 (12.6)
Grade		
Grade I	291 (3.4)	136 (3.8)
Grade II	4,223 (50.0)	1,826 (50.4)
Grade III	3,870 (45.8)	1,639 (45.3)
Grade IV	65 (0.8)	21 (0.6)
Surgery		
No	1,952 (23.1)	785 (21.7)
Yes	6,497 (76.9)	2,837 (78.3)
Radiation		
No/unknown	6,819 (80.7)	2,928 (80.8)
Yes	1,630 (19.3)	694 (19.2)
Chemotherapy		
No/unknown	7,626 (90.3)	3,288 (90.8)
Yes	823 (9.7)	334 (9.2)

Data are presented as n (%).

in SQCC patients post-surgery in their study of N0-N1 NSCLC (8). Given the wide tumor staging inclusion and varied treatment approaches in the aforementioned studies, alongside clinical feature disparities, the present study specifically included only T1-T2N0M0 stage patients who underwent surgery for prognosis comparison. The conclusion drawn was that among early-stage lung cancer patients treated solely with surgery, there was no statistically significant difference in disease-specific survival, but OS favored lung AC over SQCC.

For patients with early-stage NSCLC who are not eligible for surgery or decline it, stereotactic body radiation therapy (SBRT) is often the preferred treatment option (2,22,25). SBRT has demonstrated over 90% local control at 3 years and favorable survival rates (26,27). Currently, radiation doses do not vary based on histological subtypes. Guidelines from the European Society for Radiotherapy and Oncology and the ESTRO Guidelines Committee [former Advisory Committee for Radiation Oncology Practice (ACROP)] recommend doses of 15 Gy ×3 fractions for peripheral lesions, and a maximum tolerated dose of 18 Gy ×3 fractions for patients without significant comorbidities and with a long life expectancy (28). In cervical cancer, SQCC regresses more rapidly, is more sensitive to radiation, and has a better prognosis compared to AC (29-32). Whether these differences exist in lung cancer remains debated. Some studies, like that by Mak *et al.* (33), which analyzed 75 peripheral lung cancer patients treated with SBRT, found no association between histology and local recurrence or distant metastasis. Another study involving 91 stage I NSCLC patients treated with SBRT suggested that

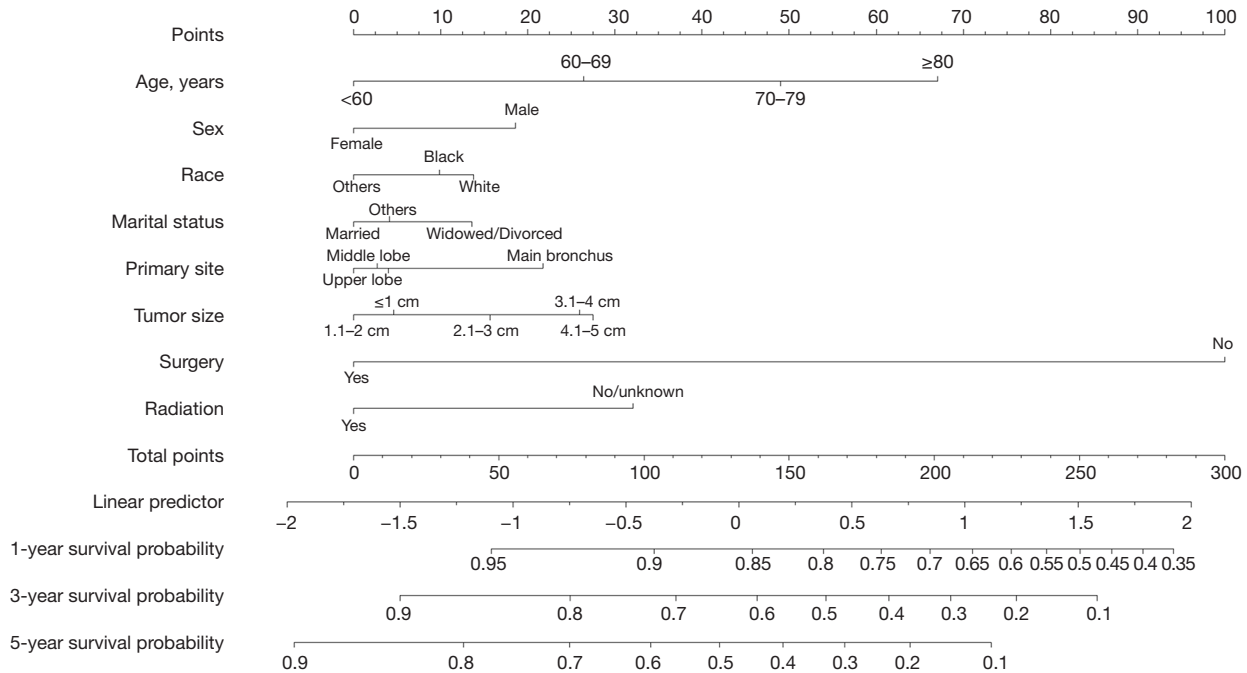

Figure 5 Nomogram for predicting 1-, 3- and 5-year overall survival in patients with T1-T2N0M0 lung squamous cell carcinoma.

while SQCC regressed faster than AC, especially at 2 and 4 months post-SBRT, there was no significant difference in 3-year and 4-year local control rates (34). Research on T1-T2N0M0 stage lung cancer patients treated with SBRT (35) indicated that SQCC patients appeared to derive more survival benefit compared to AC patients. However, other studies suggest that AC benefits more from radiation than SQCC. Woody *et al.* (3), studying lung cancer patients (T1-T3N0M0 AJCC 7th edition) treated with SBRT, reported that SQCC had twice the local failure rate compared to AC, with a 3-year cumulative local failure rate of approximately 19% for SQCC. Numerous studies (2,36-39) have confirmed that pathological type, tumor volume, and radiation dose influence local control outcomes.

Most previous prospective and retrospective studies did not use PSM and did not report the direct impact of SBRT on survival in different pathological subtypes. This study used PSM to explore differences in prognosis between SQCC and AC after exclusive radiotherapy, revealing poorer LCSS and OS outcomes for SQCC compared to AC. The reasons for these conclusions remain unclear, genetic diversity (40,41) and microenvironmental characteristics (42) may explain such differences. For instance, the three most common mutations (>50%) in AC are Kirsten rat sarcoma viral oncogene homologue (KRAS), epidermal growth factor receptor (EGFR), and anaplastic lymphoma kinase (ALK), whereas phosphatase and tensin homolog (PTEN), fibroblast growth factor receptor 1 (FGFR1), and phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) are more prevalent in SQCC (43). Studies indicate that EGFR and ALK mutations tend to be sensitive to radiotherapy (44-46), while other listed mutations appear to confer radiotherapy resistance (47-50). Furthermore, programed-cell death ligand 1 (PD-L1) expression in SQCC appears higher than in AC, and high PD-L1 expression can inhibit T-cell activation, correlating with poorer prognosis (51). Additionally, studies demonstrate that thymidylate synthase (TS) promotes deoxyribonucleic acid (DNA) synthesis, enhancing cell proliferation. Lower TS levels in AC may reflect lower DNA repair capacity, potentially leading to a higher response to radiotherapy (52,53), and correlating with better clinical outcomes (54). Finally, high glucose metabolism reduces tumor antioxidant capacity, which is associated with radiotherapy resistance (55) Compared to AC, SQCC exhibits higher expression of hypoxia-inducible factor-1α (HIF-1α) (56), lower vascular density, restricted oxygen diffusion, and higher glycolysis rates at messenger ribonucleic acid(mRNA) and protein levels (42) all of which impact the tumor microenvironment, potentially

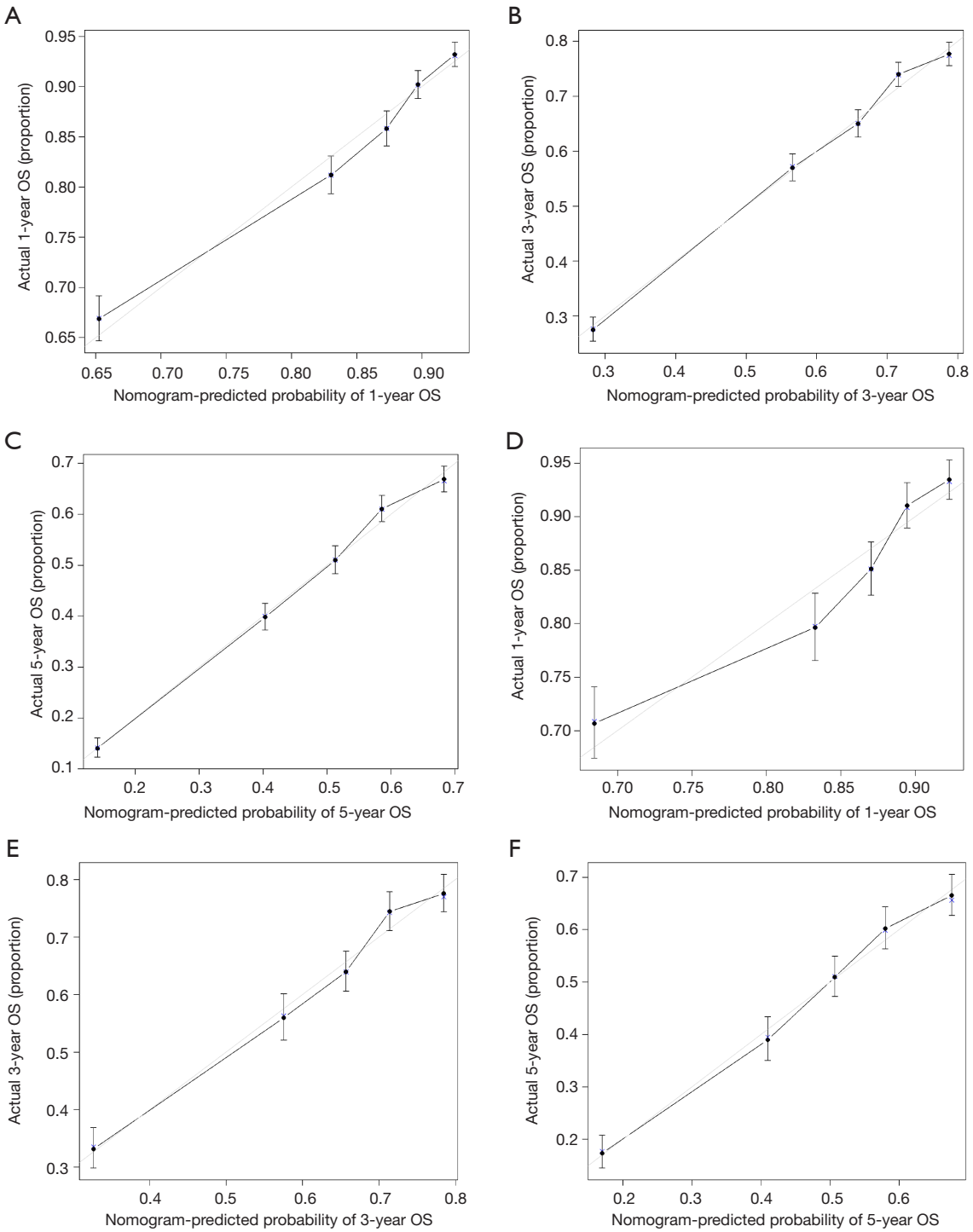

Figure 6 Calibration curves of nomograms for predicting 1-, 3- and 5-year OS in patients with lung squamous cell carcinoma: (A) Calibration curve for predicting 1-year OS in the training set. (B) Calibration curve for predicting 3-year OS in the training set. (C) Calibration curve for predicting 5-year OS in the training set. (D) Calibration curve for predicting 1-year OS in the validation set. (E) Calibration curve for predicting 3-year OS in the validation set. (F) Calibration curve for predicting 5-year OS in the validation set. OS, overall survival.

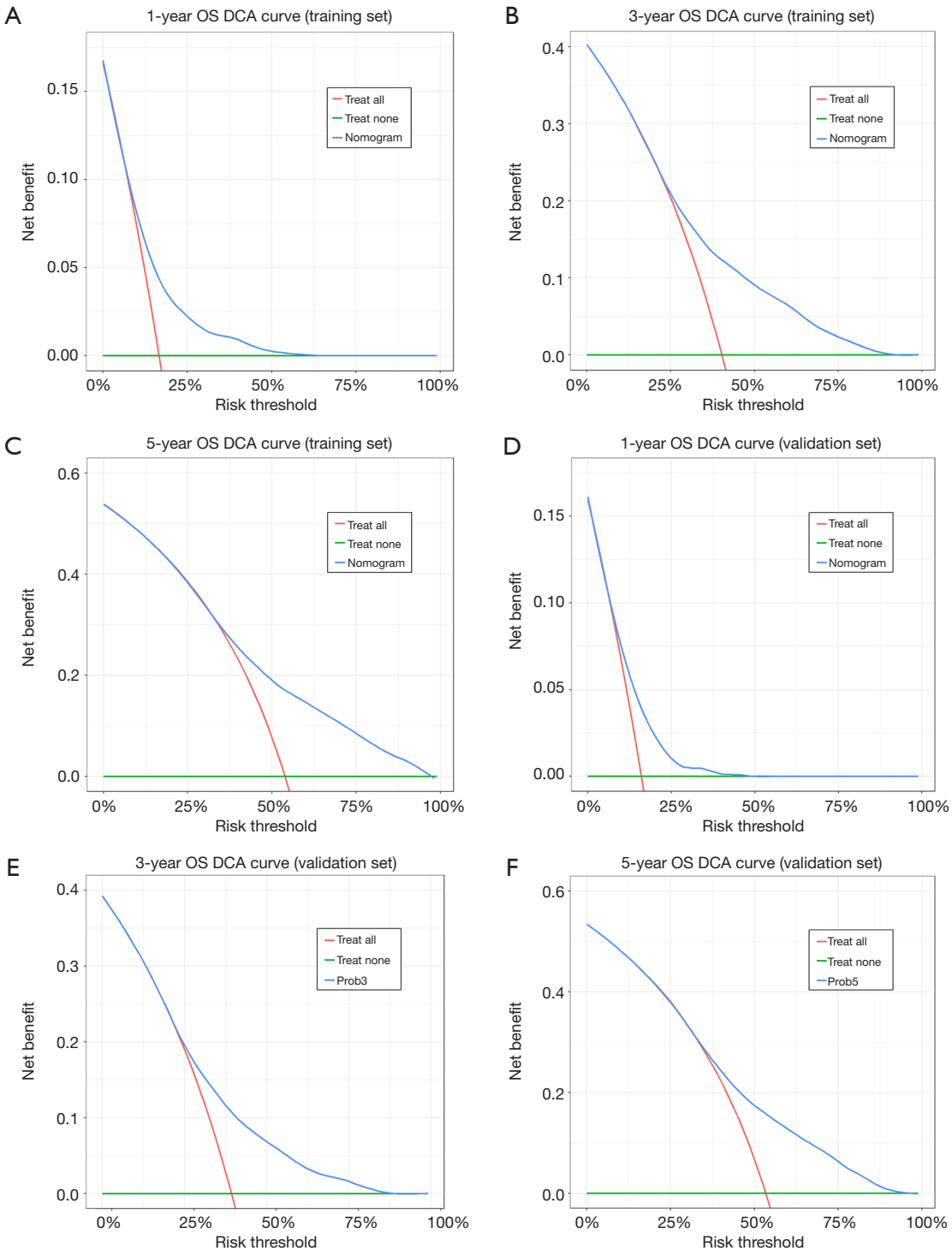

Figure 7 DCA curves of nomograms for predicting 1-, 3- and 5-year OS of patients with lung squamous cell carcinoma: (A) DCA curve of predicting 1-year OS in the training set; (B) DCA curve of predicting 3-year OS in the training set; (C) DCA curve of predicting 5-year OS in the training set; (D) DCA curve for predicting 1-year OS in the validation set; (E) DCA curve of predicting 3-year OS in the validation set; (F) DCA curve of predicting 5-year OS in the validation set. DCA, decision curve analysis; OS, overall survival.

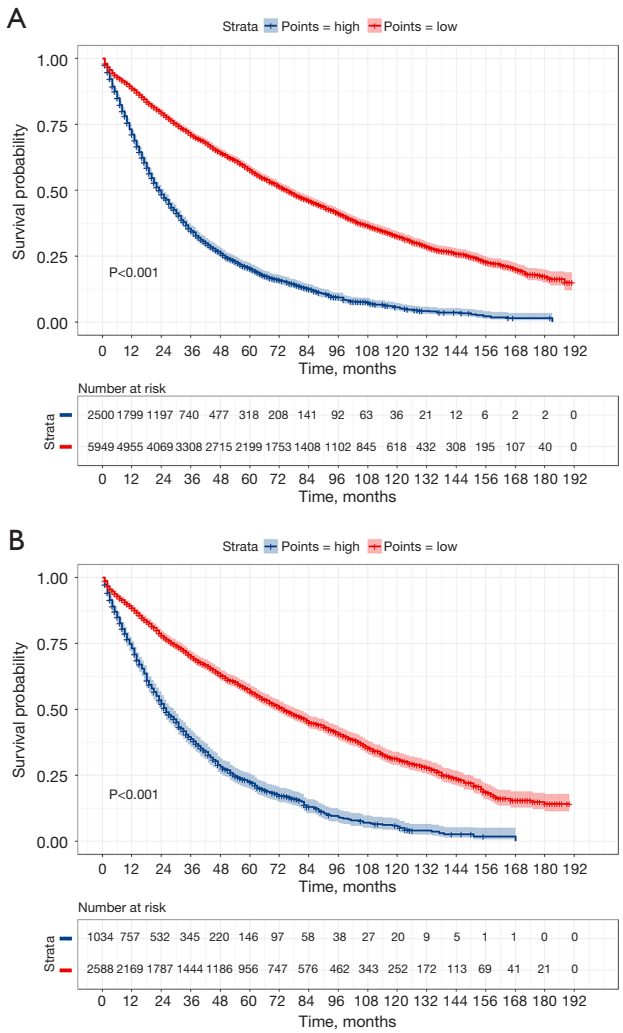

Figure 8 Kaplan-Meier curves of OS in low-risk and high-risk patients in (A) training set and (B) validation set. OS, overall survival.

contributing to lower local control rates in SQCC (57). These features collectively suggest enhanced radiotherapy resistance in SQCC.

This study represents the largest investigation to date on prognostic outcomes in early-stage lung cancer across different histological types after rigorous matching, focusing exclusively on radiotherapy. The observed differences in outcomes between these histological types suggest that a standardized radiotherapy protocol for early-stage lung cancer may be insufficient. Instead, optimizing treatment based on histological subtypes might be more beneficial. This finding has significant clinical implications. Currently, limited research suggests that tailoring treatments based on histology could enhance survival rates in NSCLC patients. For instance, radiotherapy resistance related to genes like KRAS and TP53 might be mitigated by increasing radiation doses (58). Higher doses could potentially reduce the outcome disparities between AC and SQCC. Hörner-Rieber *et al.* (36) reported that SQCC patients undergoing SBRT with a central planning-target volume (PTV) total dose ≥150 Gy (equivalent dose in 2 Gy fractions, EQD2) did not show significant differences in local control (P=0.36), and different pathologies did not significantly affect distant metastases (P=0.83). Liu *et al.* (2) found that, compared to AC, SQCC requires higher radiation doses for optimal local control. Similar research indicates that while SQCC of the lung tends to exhibit poorer local control with radiotherapy compared to AC, this can be overcome with higher biologically equivalent doses (BEDs) (3,59).

Additionally, studies on cervical cancer radiotherapy suggest that AC patients have poorer OS and disease-free survival (DFS) compared to SQCC patients (29-32). This contradicts the prognosis observed in early-stage lung cancer patients receiving radiotherapy. Therefore, another significant aspect of this study is that the histological subtypes of SQCC and AC may exhibit varying prognostic responses to radiotherapy depending on the primary tumor site.

Analysis of prognostic factors and nomograms for T1-T2N0M0 stage lung SQCC patients

This study conducted single-factor and multi-factor Cox regression analyses to investigate prognostic factors for T1-T2N0M0 stage lung SQCC patients. The results indicate that age, gender, race, marital status, tumor location, tumor size, radiotherapy, and surgery are independent factors influencing OS in early-stage lung SQCC patients. These findings are consistent with previous reports (13,60-65). By integrating various prognostic factors, nomograms can generate individual probabilities of clinical events to aid in clinical decision-making (10). Due to significant clinical and pathological differences between AC and SQCC, the current TNM staging system used for treatment and prediction appears broad. Therefore, we specifically categorized lung cancer patients and developed refined nomograms that incorporate multiple clinical variables to provide personalized predictions of 1-, 3-, and 5-year survival rates for each patient. Validation using C-index, calibration curves, and DCA demonstrated its predictive capability.

Limitations

There are several limitations in this study. Firstly, it is retrospective in nature, and inherent selection bias is unavoidable. Secondly, many variables are lacking in the SEER database, including smoking history, physical condition, comorbidities, tumor complications, details of chemotherapy regimens and cycles, radiation dosage/volume, surgical complications, genetic mutations, and targeted therapies, among others. This restricts further detailed exploration of early-stage lung cancer. Thirdly, although the nomograms developed in this study demonstrated good discrimination and calibration, validation was limited to internal data only, lacking external validation with independent datasets.

Conclusions

In summary, for stage T1-T2N0M0 NSCLC patients, surgery or radiation therapy can improve LCSS and OS. However, the impact of chemotherapy alone on LCSS and OS in early-stage lung cancer was not statistically significant. Furthermore, the prognosis of early-stage lung SQCC and AC is different under the same treatment mode. When only surgical treatment was performed, the difference in LCSS between the two cancers was not statistically significant. Lung SQCC had a worse LCSS than lung AC when treated with radiation alone. This finding suggests that radiation therapy needs to be optimized based on histological subtypes. Overall, early-stage lung SQCC has a worse OS compared to AC. Factors such as age, gender, race, marital status, tumor location, tumor size, receipt of radiotherapy, and receipt of surgery are independent prognostic factors for OS in T1-T2N0M0 SQCC patients. This study further developed nomograms to predict the 1-, 3-, and 5-year survival rates of lung SQCC patients. This model can assist clinicians in effectively assessing the disease and making treatment decisions.

In the era of personalized medicine, even when formulating treatment strategies for early-stage lung cancer patients, pathological differences should be considered separately for analysis, aiming to provide more accurate diagnosis and treatment in the future.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1602/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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