Am J Cancer Res 2024;14(6):2957-2970
www.ajcr.us /ISSN:2156-6976/ajcr0155935

Original Article

Statin therapy enhances survival in unresectable stage III lung squamous cell carcinoma with concurrent chemoradiotherapy

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Received February 17, 2024; Accepted May 24, 2024; Epub June 15, 2024; Published June 30, 2024

Abstract: To evaluate the impact of statin use on overall survival and lung cancer-specific survival in patients with unresectable stage III lung squamous cell carcinoma (LSCC) undergoing standard concurrent chemoradiotherapy (CCRT). Using data from the Taiwan Cancer Registry Database and National Health Insurance Research Database, this propensity score matching cohort study analyzed the influence of statin use during CCRT on overall survival and lung cancer-specific survival. Statin use during CCRT was independently associated with significant improvements in overall survival and lung cancer-specific survival. The adjusted hazard ratio (95% CI) for all-cause mortality in the statin group versus the non-statin group was 0.60 (0.53-0.68, P < 0.0001). Similarly, the adjusted hazard ratio for lung cancer-specific mortality in the statin group versus the non-statin group was 0.61 (95% CI, 0.54-0.70, P < 0.0001). Pravastatin and fluvastatin exhibited the greatest potential in reducing lung cancer-specific mortality among statins, with rosuvastatin following closely behind. Atorvastatin demonstrated comparable effectiveness, while simvastatin and lovastatin displayed lower efficacy in this regard. Furthermore, a dose-response relationship was observed, with higher cumulative defined daily doses and greater daily intensity of statin use associated with reduced mortality. Our study provides evidence that statin use during CCRT for unresectable stage III LSCC is associated with significant improvements in overall survival and lung cancer-specific survival. Pravastatin showed the highest potential for reducing lung cancer-specific mortality among statins, followed by rosuvastatin. Atorvastatin and fluvastatin exhibited similar effectiveness, while simvastatin and lovastatin demonstrated lower efficacy. The dose-response relationship showed higher statin utilization in reducing lung cancer-specific mortality.

Keywords: Lung squamous cell carcinoma, unresectable, statin, concurrent chemoradiotherapy, mortality

Introduction

Lung squamous cell carcinoma (LSCC) accounts for a significant proportion of non-small cell lung cancer cases worldwide, with an estimated incidence ranging from 25% to 30% [1]. Unlike other histological subtypes, LSCC is characterized by a scarcity of driver mutations, limiting the availability of targeted therapies such as tyrosine kinase inhibitors [2]. As a result, the standard treatment options for these patients typically involve surgery, chemotherapy, or concurrent chemoradiotherapy (CCRT) [3]. Immunotherapy, although an emerg-

https://doi.org/10.62347/NZHY5175

ing treatment modality, is not yet considered a first-line therapy and is often associated with high costs, which might be not covered by Health Insurance [3, 4]. Many lung cancer patients are diagnosed at advanced stages, often in the absence of discernible symptoms, leading to a higher proportion of unresectable cases [5, 6]. These patients frequently present with clinical evidence of mediastinal lymph node involvement (N2) or contralateral mediastinal or hilar lymph node metastasis (N3), making surgical intervention unfeasible [3, 7]. The NCCN guidelines recommend CCRT as the standard treatment approach for unresectable stage III LSCC patients without distant metastasis [3]. In Taiwan, LSCC exhibits a notable prevalence, accounting for approximately 20% to 30% of all non-small-cell lung cancer cases in the region [6]. However, despite the utilization of standard CCRT, the prognosis for patients with unresectable stage III LSCC remains exceedingly poor [8]. Therefore, there is an urgent need to explore novel strategies aimed at improving the survival outcomes for this specific subset of patients undergoing CCRT.

Statin usage has garnered considerable attention for its potential anticancer effects across various cancer types [9-14]. Specifically, in lung cancer [15], statins have demonstrated anticancer effects, with preclinical studies indicating their protective effects against radiation-induced toxicity in normal lung cells and tissues [16-19]. Furthermore, statins induce tumor apoptosis in squamous cell carcinomas (SCC) through two pathways: 1) activation of the integrated stress response, and 2) inhibition of ligand-induced activation of the epidermal growth factor receptor [20]. This dual action resulted in stabilized end-stage disease in 23% of SCC patients treated with statins [21]. Statins exert anticancer effects by inhibiting HMG-CoA reductase and mevalonate synthesis, crucial for producing isoprenoid molecules essential for cellular proteins like Ras and Rho [15, 22, 23]. These proteins are vital for cell survival activities such as proliferation, differentiation, and apoptosis [24-32]. By altering these proteins' functions, statins reduce cell viability, induce apoptosis, and enhance antitumor effects when combined with platinum or radiation therapy [24-32]. These properties make statins promising antiproliferative, pro-apoptotic, anti-invasive, and radio-sensitizing agents [11, 12]. These findings highlight the potential benefits of statins in improving oncologic outcomes, including reducing cancer-related mortality and treatment-related toxicity. However, there is currently a lack of clinical studies investigating the effects of statins in LSCC patients undergoing CCRT. Furthermore, data regarding the comparative efficacy of different types of statins and the dose-response relationship of statin use on mortality in LSCC patients receiving CCRT remain unclear. Additionally, the optimal dosage and duration of daily statin use for lung cancer patients undergoing CCRT have yet to be determined.

Given the persistently poor survival outcomes in LSCC patients undergoing CCRT and the potential clinical benefits of statin use in this population, we aimed to address this unresolved issue by conducting a real-world study utilizing a propensity score matching (PSM) design. This approach aimed to simulate a randomized controlled trial (RCT) and allowed us to evaluate the effects of statin use, different types of statins, daily statin intensity, and the cumulative dose-dependent effect of statin use on mortality in LSCC patients receiving CCRT.

Patients and methods

Study design and data sources

This cohort study utilized data from two primary sources: the Taiwan Cancer Registry Database (TCRD) and Taiwan's National Health Insurance Research Database (NHIRD). The study focused on individuals diagnosed with LSCC between January 1, 2012, and December 31, 2018. The index date, which marked the initiation of standard CCRT for LSCC, served as the study's starting point, and the follow-up period extended until December 31, 2020. The TCRD, managed by the Collaboration Center of Health Information Application, provided comprehensive information on cancer patients, including clinical stage, treatment details, chemotherapy regimens, doses, pathology, radiation therapy, and protocols [14, 33-35]. The study protocols were thoroughly reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Inclusion and exclusion criteria

The study included patients who met specific eligibility criteria: they had to be 18 years or older, have a confirmed diagnosis of LSCC, be in advanced clinical stage III without metastasis according to the eighth edition of the AJCC, and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with a history of previous cancer, distant metastasis, missing sex data, age below 18, unclear staging, unknown cigarette smoking or alcohol use, or non-squamous cell carcinoma histology were excluded from the study. Clinical N0-1 cases were also excluded, as these patients may have more suitable treatment options with surgery as the initial approach rather than CCRT being the first-line therapy [3].

Standard CCRT for LSCC was defined as the administration of platinum-based chemotherapy, such as cisplatin or carboplatin, in combination with intensity-modulated radiation therapy (IMRT). The total radiation dose administered was 60-70 Gy, delivered in fractions of 2.0 Gy [3]. In our study, the minimum irradiation dose was set at 60 Gy [3]. The presence of comorbidities was assessed using the Charlson comorbidity index (CCI), considering only comorbidities documented within 6 months prior to the index date. These comorbidities were categorized using the corresponding codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or ICD-10-CM, starting from the patient's initial inpatient visit or after a minimum of two outpatient visits.

Statin use after CCRT for LSCC

In this study, statin prescriptions were identified using the Anatomical Therapeutic Chemical (ATC) classification system within the NHIRD Pharmaceutical subsidies, which provided access to pharmaceutical claim data [36]. The primary focus was on lipophilic statins (atorvastatin, fluvastatin, lovastatin, simvastatin, and pitavastatin) and hydrophilic statins (pravastatin and rosuvastatin). To be categorized as statin users, patients needed to have received a minimum of 28 cumulative defined daily doses (cDDDs) of statins during the course of definitive CCRT for LSCC. Conversely, patients who did not use any statins (0 cDDDs) during the entire follow-up period were considered statin non-users. After the CCRT period, the use of statins in the statin use group could continue, and the association between cDDD and the hazard ratio of mortality was analyzed. The patients were further divided into subgroups based on quartiles (Q1, Q2, Q3, Q4) of cDDD to assess the dose-response effects of statin use on oncologic outcomes in unresectable stage III LSCC patients undergoing CCRT. All analyses were adjusted for the covariates listed in **Table 1** to mitigate potential biases. To minimize confounding effects, individuals who had initiated statin therapy prior to the index date were excluded from the analysis. Including such patients could introduce bias due to their prolonged history of hyperlipidemia, which might lead to an increased risk of cardiovascular complications and ultimately contribute to higher all-cause mortality rates. In order to mitigate potential confounders, our study specifically targeted patients who initiated statin therapy during CCRT. These patients represent newly diagnosed individuals with hyperlipidemia and a shorter disease duration. As a result, their cardiovascular risk profile is comparatively lower when compared to individuals with a longer history of statin usage. Additionally, crossover use of different statin classes was excluded from the cohort to better understand the specific effects of individual statin classes on survival outcomes for unresectable stage III LSCC patients undergoing definitive CCRT. Although these inclusion criteria may have limited the sample size, only patients who initiated statin use on the first day of CCRT were strictly included. Considering that the CCRT period spanned approximately 7-8 weeks, patients had the potential to accumulate a minimum of 28 cDDDs of statin use during this timeframe.

Furthermore, we assessed the daily intensity of statin use by calculating the average dose of statin, derived from dividing the defined daily dose (DDD) by the total number of days in the prescription. The intensity of statin use was categorized into two groups based on the average daily dose: below 1 DDD and above 1 DDD. We also examined the relationship between hazard ratios of all-cause mortality, lung cancer-specific mortality, and the DDD of statin use to determine the optimal daily intensity of statin use that would effectively reduce mortality in patients with LSCC undergoing definitive CCRT.

Table 1. Comparison of characteristics between patients with and without statin use following standard definitive CCRT for advanced stage III lung squamous cell carcinoma

	Before PSM					After PSM				
	Statins nonusers		Statin users			Statin nonusers		Statin users		
	N=1,577		N=390		*ASMD*	N=711		N=389		*ASMD*
	N	%	N	%		N	%	N	%	
Age (mean ± SD), years-old	63.18 ± 12.63		69.19 ± 10.56			67.98 ± 10.88		69.14 ± 10.52		
Age, median (IQR, Q1, Q3)	63.82 (54.27, 72.62)		70.10 (61.37, 77.12)			68.63 (60.00, 75.84)		70.08 (61.37, 77.12)		
Age group, years					0.4910					0.0910
≤ 50	423	26.82%	41	10.51%		71	9.99%	41	10.54%	
51-60	411	26.06%	103	26.41%		210	29.54%	103	26.48%	
61-70	451	28.60%	116	29.74%		224	31.50%	116	29.82%	
≥ 70	292	18.52%	130	33.33%		206	28.97%	129	33.16%	
Sex					0.0187					0.0139
Female	568	36.02%	144	36.92%		268	37.69%	144	37.02%	
Male	1,009	63.98%	246	63.08%		443	62.31%	245	62.98%	
Income (NTD)					0.1570					0.0430
Low income	10	0.63%	4	1.03%		5	0.70%	3	0.77%	
Financially dependent	477	30.25%	139	35.64%		261	36.71%	139	35.73%	
≤ 20,000	565	35.83%	138	35.38%		244	34.32%	138	35.48%	
20,001-30,000	344	21.81%	73	18.72%		140	19.69%	73	18.77%	
30,001-45,000	123	7.80%	21	5.38%		37	5.20%	21	5.40%	
> 45,000	58	3.68%	15	3.85%		24	3.38%	15	3.86%	
Urbanization					0.0967					0.0278
Rural	498	31.58%	106	27.18%		185	26.02%	106	27.25%	
Urban	1,079	68.42%	284	72.82%		526	73.98%	283	72.75%	
AJCC clinical stage, 8th edition					0.4860					0.0002
IIIA	501	31.77%	132	33.85%		241	33.89%	131	33.68%	
IIIB	556	35.26%	214	54.87%		391	54.99%	214	55.01%	
IIIC	520	32.97%	44	11.28%		79	11.11%	44	11.31%	
Current Cigarette Smoking	647	41.03%	194	49.74%	0.1756	342	48.10%	193	49.61%	0.0302
Current Alcohol consumption	229	14.52%	55	14.10%	0.0120	105	14.77%	55	14.14%	0.0179
CCI Scores										
Mean (SD)	4.48 ± 3.04		4.54 ± 3.20			4.45 ± 3.08		4.52 ± 3.19		
Median (IQR, Q1-Q3)	6.00 (1.00, 7.00)		6.00 (1.00, 7.00)			6.00 (1.00, 7.00)		6.00 (1.00, 7.00)		
CCI Scores					0.0549					0.0274
0	232	14.71%	50	12.82%		98	13.78%	50	12.85%	
≥ 1	1,345	85.29%	340	87.18%		613	86.22%	339	87.15%	
Statin										
Non use	1,577	100.00%	0	0.00%		711	100.00%	0	0.00%	
Lipophilic statins										
Atorvastatin	0	0.00%	124	31.79%		0	0.00%	123	31.62%	
Lovastatin	0	0.00%	57	14.62%		0	0.00%	57	14.65%	
Simvastatin	0	0.00%	78	20.00%		0	0.00%	78	20.05%	
Fluvastatin	0	0.00%	39	10.00%		0	0.00%	39	10.03%	
Hydrophilic statins										
Rosuvastatin	0	0.00%	68	17.44%		0	0.00%	68	17.48%	
Pravastatin	0	0.00%	24	6.15%		0	0.00%	24	6.17%	
cDDD										
Non use	1,577	100.00%	0	0.00%		711	100.00%	0	0.00%	
Q1	0	0.00%	99	25.38%		0	0.00%	98	25.19%	
Q2	0	0.00%	96	24.62%		0	0.00%	96	24.68%	
Q3	0	0.00%	98	25.13%		0	0.00%	98	25.19%	
Q4	0	0.00%	97	24.87%		0	0.00%	97	24.94%	
DDD										
≤ 1	0	0.00%	334	85.64%		0	0.00%	333	85.60%	
> 1	0	0.00%	56	14.36%		0	0.00%	56	14.40%	

Oncologic Outcomes					*P*-Value					*P*-Value
All-Cause Death	1,371	86.94%	311	79.74%	0.0003	618	86.92%	310	79.69%	0.0016
Lung Cancer death	1,289	81.74%	296	75.90%	0.0009	579	81.43%	296	76.09%	0.0357

Abbreviations: CCRT, Concurrent chemoradiotherapy; AJCC, American Joint Committee on Cancer; PSM, Propensity score matching; CCI, Charlson comorbidity index; cDDDs, cumulative defined daily doses; DDD, defined daily doses; SD, standard deviation; IQR, interquartile range; ASMD, absolute standardized mean differences; NTD, new Taiwan dollars.

Propensity score matching

To minimize the influence of potential confounding factors when comparing survival outcomes between the statin use and non-statin use groups, we employed PSM to ensure comparability. PSM was conducted based on several variables, including age, sex, AJCC clinical stage, income levels, urbanization, differentiation, cigarette smoking habits, alcohol consumption habits, and CCI scores (as outlined in **Table 1**). The statin use and non-statin use groups were matched in a 1:2 ratio using the greedy matching method with a caliper of 0.1 [37]. Continuous variables were reported as means ± standard deviations, as appropriate.

Outcome measures

The primary aim of this study was to evaluate the effect of statin use during standard definitive CCRT on overall mortality rates in patients with unresectable stage III LSCC. The secondary objective was to examine the incidence of lung cancer-specific mortality in relation to statin use.

Statistical analysis

To assess the relationship between statin use during the CCRT period and survival outcomes in patients with unresectable stage III LSCC who underwent standard CCRT, we conducted a comprehensive analysis. To control for potential confounding variables, we utilized time-varying Cox regression models and adjusted for factors listed in **Table 1**. We employed a time-dependent Cox hazard model to compare mortality rates between statin users and non-users, considering the aforementioned confounding factors. The status of statin prescriptions was evaluated every 3 months as a time-dependent variable, ensuring that "event-free" person-times of users without statin prescriptions were classified as unexposed follow-up times to avoid bias. Moreover, we examined the risk of mortality associated with individual statins. The Kaplan-Meier method was used to estimate mortality rates, and differences between statin users and non-users were assessed using the stratified log-rank test. Additionally, we evaluated mortality rates in relation to different cDDD of statin use, and differences between statin users at varying dosage levels and non-users were assessed using the stratified log-rank test. We also estimated the cDDD, DDD, and hazard ratio of lung cancer-specific mortality in patients undergoing CCRT who received statins compared to non-users. All statistical analyses were performed using SAS version 9.4.

Results

Clinicopathological characteristics

A total of 1,967 patients with stage III unresectable LSCC who underwent standard CCRT were enrolled in the study. Among them, 1,577 patients were included in the non-statin group, while 390 patients were in the statin group. Baseline characteristics, as shown in **Table 1**, indicated that the statin group had a higher proportion of elderly individuals, a larger percentage of low-income individuals, a higher proportion of urban residents, a lower frequency of advanced stages (IIIC), and a higher prevalence of current congregate smoking compared to the non-statin group. After PSM, the analysis included a total of 1,100 unresectable stage III LSCC patients who received definitive CCRT, with 389 patients in the statin group and 711 patients in the non-statin group. The matching process successfully balanced all confounding factors between the two groups (all ASMD < 0.1) [37]. The median follow-up duration was 3.12 years. After PSM, the crude rates of all-cause mortality were 86.92% in the matched non-statin group and 79.69% in the matched statin group (P=0.0016). Similarly, the rates of lung cancer-specific mortality were 81.43% in the matched non-statin group (**Table 1**) and 76.09% in the matched statin group (P=0.0357).

Table 2. Cox proportional hazards regression model of all-cause mortality in PSM patients with and without statin use following standard definitive CCRT for stage III lung squamous cell carcinoma

	All-Cause Death			
	Crude HR (95% CI)	*P*-value	aHR* (95% CI)	*P*-value
Statin (ref. no statin use)				
Statin use	0.70 (0.59, 0.82)	< 0.0001	0.60 (0.53, 0.68)	< 0.0001
Statin Class (ref. no statin use)				
Hydrophilic statins				
Pravastatin	0.65 (0.41, 1.02)	0.0605	0.45 (0.33, 0.61)	< 0.0001
Rosuvastatin	0.76 (0.56, 1.02)	0.0709	0.59 (0.47, 0.74)	< 0.0001
Lipophilic statins				
Fluvastatin	0.40 (0.32, 0.87)	0.0064	0.39 (0.35, 0.76)	< 0.0001
Simvastatin	0.68 (0.51, 0.89)	0.0051	0.62 (0.52, 0.75)	< 0.0001
Lovastatin	0.77 (0.56, 1.06)	0.1045	0.70 (0.57, 0.86)	0.0006
Atorvastatin	0.70 (0.55, 0.89)	0.0031	0.59 (0.50, 0.70)	< 0.0001
cDDD of Statin (ref. no statin use)				
Q1	0.93 (0.72, 1.19)	0.5545	0.79 (0.67, 0.93)	0.0053
Q2	0.71 (0.55, 0.91)	0.0061	0.62 (0.52, 0.73)	< 0.0001
Q3	0.60 (0.46, 0.78)	0.0001	0.48 (0.36, 0.53)	< 0.0001
Q4	0.58 (0.45, 0.76)	< 0.0001	0.44 (0.40, 0.59)	< 0.0001
DDD of Statin (ref. no statin use)				
≤ 1	0.72 (0.49, 0.89)	0.0046	0.61 (0.51, 0.82)	0.0022
> 1	0.57 (0.37, 0.70)	0.0002	0.52 (0.39, 0.69)	< 0.0001

Abbreviations: CCRT, Concurrent chemoradiotherapy; PSM, Propensity score matching; CI, Confidence interval; aHR, Adjusted hazard ratio; HR, hazard ratio; cDDDs, cumulative defined daily doses; DDD, defined daily doses; ref., reference group. *Adjustment of age, sex, AJCC clinical stage, income levels, urbanization, differentiation, cigarette smoking habits, alcohol consumption habits, and CCI scores.

All-cause mortality

Statin use following standard CCRT emerged as a significant and independent prognostic factor for all-cause mortality in patients with unresectable stage III LSCC. The adjusted hazard ratio (aHR) with a 95% confidence interval (CI) for all-cause mortality in the statin group compared to the non-statin group was 0.60 (0.53-0.68, P < 0.0001), as shown in **Table 2**. Among the different classes of statins, hydrophilic statins, specifically pravastatin and rosuvastatin, exhibited favorable aHRs (95% CI) of 0.45 (0.33-0.61) and 0.59 (0.47-0.74), respectively, compared to non-statin use. Lipophilic statins, including fluvastatin, atorvastatin, simvastatin, and lovastatin, demonstrated aHRs (95% CI) of 0.39 (0.35-0.76), 0.59 (0.50-0.70), 0.62 (0.52-0.75), and 0.70 (0.57, 0.86), respectively, in relation to non-statin use. In terms of cDDD, the aHRs (95% CI) for all-cause mortality in the fourth, third, second, and first quartiles of cDDD were 0.44 (0.40-0.59), 0.48 (0.36-0.53), 0.62 (0.52-0.73), and 0.79 (0.67-0.93), respectively (The *p*-value for trend < 0.0001). For DDD, the aHR (95% CI) was 0.50 (0.33-0.74) for DDD > 1 and 0.61 (0.51-0.82) for DDD ≤ 1. The *p*-values for the trend of cDDD and DDD were all < 0.0001, indicating a clear dose-response relationship between statin use and all-cause mortality.

Lung cancer-specific mortality

The use of statins following standard CCRT showed a significant impact on reducing the risk of lung cancer-specific mortality in treated patients. The adjusted hazard ratio (aHR) for lung cancer-specific mortality in the statin group compared to the non-statin group was 0.61 (0.54-0.70) with a *P*-value of < 0.0001, as presented in **Table 3**. This favorable effect was observed across different classes of statins, including hydrophilic statins such as pravastatin and rosuvastatin, which demonstrated aHRs of 0.45 (0.33-0.62) and 0.60

Table 3. Cox proportional hazards regression model of lung cancer-specific mortality in PSM patients with and without statin use following standard definitive CCRT for stage III lung squamous cell carcinoma

	Lung Cancer-Specific Death			
	Crude HR (95% CI)	*P*-value	aHR* (95% CI)	*P*-value
Statin (ref. no statin use)				
Statin use	0.73 (0.62, 0.86)	0.0002	0.61 (0.54, 0.70)	< 0.0001
Statin Class (ref. no statin use)				
Hydrophilic statins				
Pravastatin	0.67 (0.42, 1.07)	0.0915	0.45 (0.33, 0.62)	< 0.0001
Rosuvastatin	0.79 (0.58, 1.07)	0.1289	0.60 (0.47, 0.76)	< 0.0001
Lipophilic statins				
Fluvastatin	0.33 (033, 0.91)	0.0149	0.41 (0.37, 0.80)	0.0003
Simvastatin	0.74 (0.56, 0.98)	0.0329	0.66 (0.55, 0.79)	< 0.0001
Lovastatin	0.79 (0.57, 1.1)	0.1582	0.68 (0.55, 0.84)	0.0004
Atorvastatin	0.72 (0.57, 0.93)	0.0102	0.61 (0.51, 0.72)	< 0.0001
cDDD of Statin (ref. no statin use)				
Q1	0.98 (0.76, 1.26)	0.8507	0.83 (0.70, 0.98)	0.0256
Q2	0.73 (0.56, 0.94)	0.0154	0.62 (0.52, 0.74)	< 0.0001
Q3	0.63 (0.48, 0.82)	0.0007	0.51 (0.36, 0.54)	< 0.0001
Q4	0.62 (0.47, 0.82)	0.0007	0.44 (0.41, 0.63)	< 0.0001
DDD of Statin (ref. no statin use)				
≤ 1	0.74 (0.51, 0.91)	0.0167	0.63 (0.53, 0.84)	< 0.0001
> 1	0.59 (0.39, 0.72)	0.0023	0.54 (0.41, 0.71)	< 0.0001

Abbreviations: CCRT, Concurrent chemoradiotherapy; PSM, Propensity score matching; CI, Confidence interval; aHR, Adjusted hazard ratio; HR, hazard ratio; cDDDs, cumulative defined daily doses; DDD, defined daily doses; ref., reference group. *Adjustment of age, sex, AJCC clinical stage, income levels, urbanization, differentiation, cigarette smoking habits, alcohol consumption habits, and CCI scores.

(0.47-0.76), respectively, compared to non-statin use. Lipophilic statins, including fluvastatin, atorvastatin, simvastatin, and lovastatin, exhibited aHRs of 0.41 (0.37-0.80), 0.61 (0.51-0.72), 0.66 (0.55-0.79), and 0.68 (0.55-0.84), respectively, compared to non-statin use. Additionally, a dose-dependent relationship was identified between the duration of statin use, as measured by cDDD and DDD, and the reduced risk of lung cancer-specific mortality. Higher values of cDDD and DDD were associated with a stronger reduction in risk, with *P*-values for the trend of cDDD and DDD < 0.0001, highlighting the dose-response relationship.

Kaplan-meier survival curves

There was a notable difference in the 5-year overall survival rates between patients who used statins and those who did not. In the statin use group, the 5-year overall survival rate for unresectable stage III LSCC was 19.90%, whereas in the non-statin use group, it was 14.35% (P < 0.0001; **Figure 1**). Similarly, the 5-year lung cancer-specific survival rates for patients in the statin use and non-statin use groups were 17.84% and 12.01% respectively (P < 0.0001; **Figure 2**). These findings suggest a potential association between statin use after the initiation of CCRT and improved overall survival and lung cancer-specific survival in patients with unresectable stage III LSCC undergoing CCRT. **Figure 3** further supports these conclusions, as the Kaplan-Meier curves for overall survival and lung cancer-specific survival demonstrate a dose-response relationship in patients with varying cDDD of statins following standard definitive CCRT. Additionally, higher cDDD and DDD (daily intensity of statin) were associated with lower cDDD and DDD, and a lower hazard ratio of lung cancer-specific mortality (Supplementary Figures 1 and 2).

Discussion

Emerging evidence suggests that statin drugs, commonly used for cholesterol reduction and

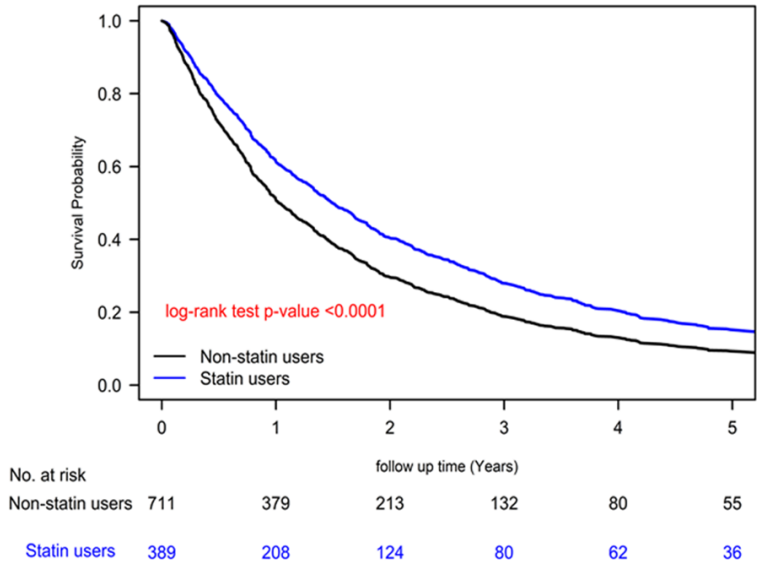

Figure 1. Kaplan-Meier analysis of overall survival in stage III lung squamous cell carcinoma patients with and without statin use following standard definitive concurrent chemoradiotherapy.

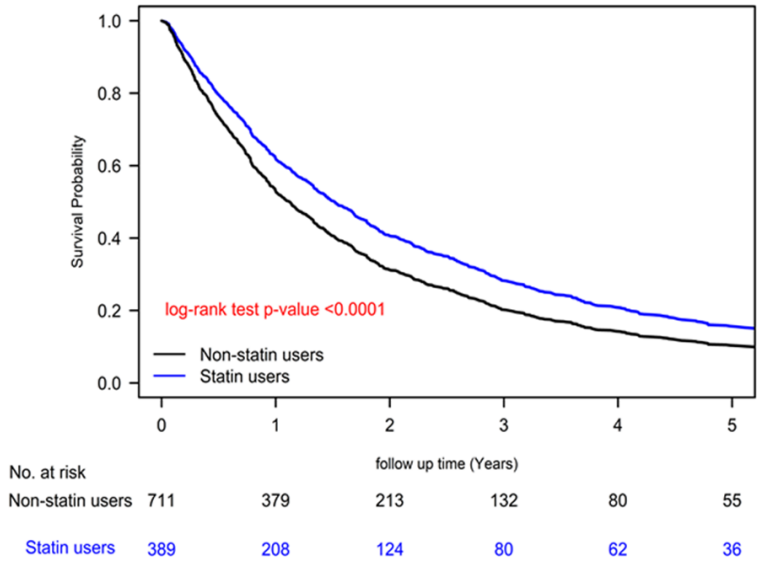

Figure 2. Kaplan-Meier analysis of lung cancer-specific survival in stage III lung squamous cell carcinoma patients with and without statin use following standard definitive concurrent chemoradiotherapy.

heart attack prevention, have potential benefits in cancer management, including improved survival and reduced toxicities associated with chemotherapy and radiotherapy [14, 15, 19, 30-32, 38, 39]. Statins possess multiple antitumor properties, inhibiting cell proliferation, angiogenesis, and invasion, and promoting apoptosis through the inhibition of downstream signaling molecules [15, 30-32, 39, 40]. These drugs also exert pleiotropic effects on genes implicated in lung cancer pathogenesis [38]. However, there is a lack of studies investigating statin use during CCRT for LSCC, specifically regarding statin types, optimal dosage, and cumulative dose. Our study aimed to address this gap by evaluating the effects of statin use during CCRT in unresectable stage III LSCC patients. We found that statin use following standard CCRT was an independent prognostic factor for all-cause mortality and lung cancer-specific mortality (**Tables 2**, **3**; **Figures 1** and **2**). Pravastatin and fluvastatin exhibited the greatest potential in reducing lung cancer-specific mortality among statins, with rosuvastatin following closely behind. Atorvastatin demonstrated comparable effectiveness, while simvastatin and lovastatin displayed lower efficacy in this regard (**Table 3**). There was a dose-response relationship between overall survival and lung cancer-specific survival based on varying cDDD of statin following CCRT. Higher cDDD and DDD were associated with lower hazard ratios for lung cancer-specific mortality (Supplementary Figures 1 and 2). Our study provides valuable insights into the optimal types and dosages of statins for unresectable stage III LSCC patients receiving CCRT, contributing to improved treatment strategies for this challenging population.

The precise mechanisms underlying the survival benefits of statin use during CCRT for advanced LSCC remain incompletely understood. Statins exert their anticancer effects by inhibiting HMG-CoA reductase and mevalonate synthesis, which are involved in the production

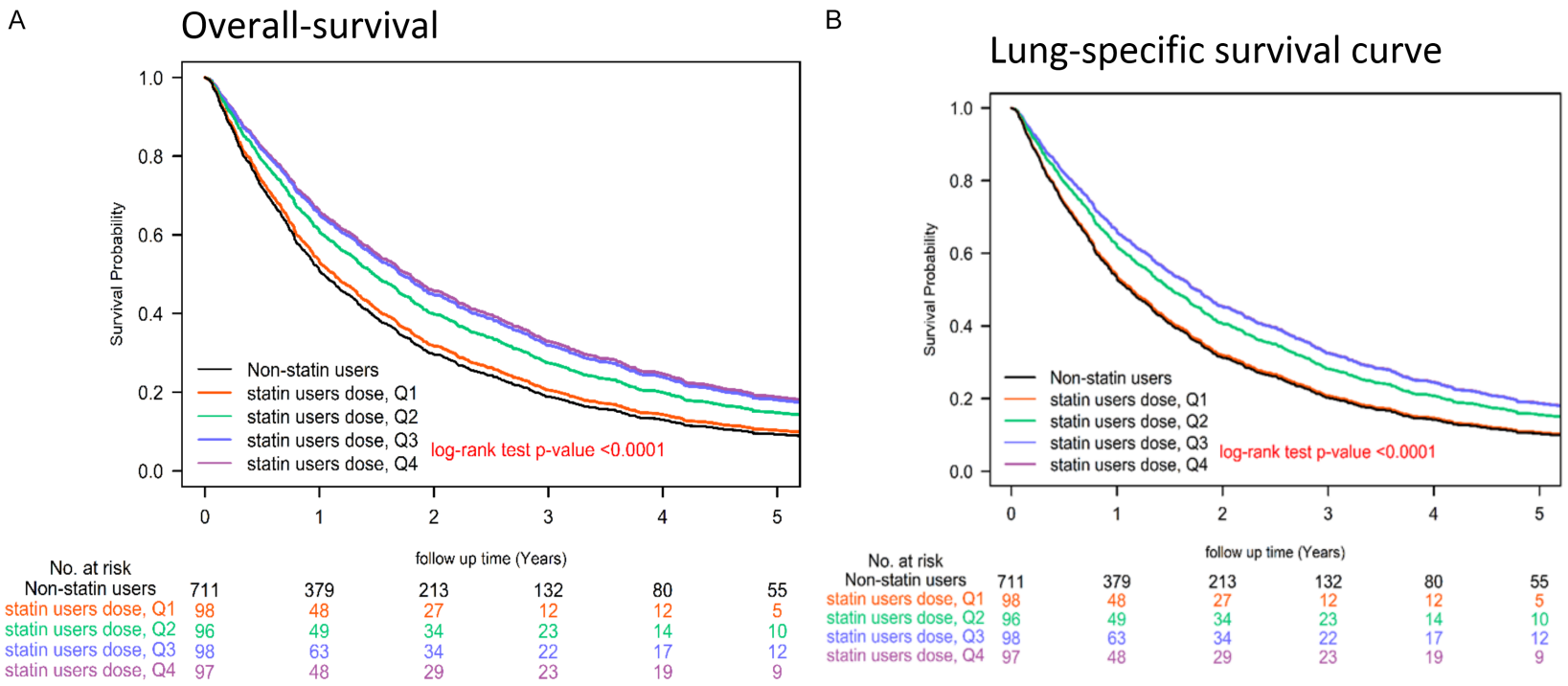

Figure 3. Kaplan-Meier curves of overall survival curves and lung cancer-specific survival curves in stage III lung squamous cell carcinoma patients with different cDDD of statin following standard definitive concurrent chemoradiotherapy.

of isoprenoid molecules essential for the function of certain cellular proteins [22, 23]. Among these proteins, Ras and Rho play critical roles in transmitting cellular signals associated with cell survival activities, including proliferation, differentiation, and apoptosis [15]. By altering the function of these proteins, statins demonstrate cytotoxic effects on cancer cells, resulting in reduced cell viability, induction of apoptosis, and enhanced antitumor effects when combined with platinum or radiation therapy [24-32]. These properties make statins promising agents with antiproliferative, pro-apoptotic, anti-invasive, and radio-sensitizing properties [11, 12]. Furthermore, statins may overcome therapy resistance, enhance the anticancer effects of CCRT, and mitigate radiation-induced toxicities, thus potentially improving overall survival and lung cancer-specific survival in patients undergoing CCRT. Radiation-induced lung toxicity, such as radiation-induced lung fibrosis, is a common complication that can contribute to mortality; however, evidence suggests that statins may alleviate radiation-induced toxicities in normal tissues [16, 19]. For instance, studies have shown that lovastatin can mitigate ionizing radiation-induced damage without causing DNA double-strand breaks in human umbilical vein endothelial cells [17], and in mice, weekly treatments of lovastatin have been found to reduce ionizing radiation-induced DNA damage in lung tissue [41]. Therefore, the incorporation of statins during CCRT not only holds potential for enhancing the anticancer effects in lung cancer but also for mitigating radiation-induced toxicity in normal lung cells. These investigations could provide valuable insights into personalized treatment approaches and optimize therapeutic outcomes for patients with unresectable stage III LSCC receiving CCRT.

This study represents the first investigation into the effects of different types of statins during the definitive CCRT period for LSCC. Among the statins evaluated, Pravastatin and fluvastatin exhibited the greatest potential in reducing lung cancer-specific mortality among statins, with rosuvastatin following closely behind. Atorvastatin demonstrated comparable effectiveness, while simvastatin and lovastatin displayed lower efficacy in this regard (**Table 3** and Supplementary Figure 3). The superiority of hydrophilic or lipophilic statins in terms of their anticancer effects, particularly in LSCC, remains unclear. Our findings provide initial evidence showing that hydrophilic statins exhibit higher anti-LSCC effects compared to lipophilic statins. These results highlight the significant reduction in all-cause and lung cancer-specific mortality associated with the use of rosuvastatin or pravastatin compared to non-users. The mechanisms underlying these effects may involve the inhibition of the proteasome pathway [42], suppression of downstream products of the mevalonate pathway [12], induction of tumor-specific apoptosis [43], and inhibition of cholesterol synthesis. Notably, statins with greater efficacy in lowering lipid profiles, such as pravastatin and rosuvastatin, may exert a more pronounced effect in reducing mortality in lung cancer patients. These findings align positively with the lipid-lowering abilities of different statins [44-46]. Additionally, pravastatin has a lower likelihood of drug interactions or muscle toxicity compared to other statins [47, 48]. Pravastatin, rosuvastatin, and fluvastatin are unlikely to cause significant pharmacokinetic drug interactions since they do not undergo metabolism via CYP3A4 [47, 48]. In other words, statins with superior lipid-lowering capabilities and fewer drug-drug interactions are more likely to exhibit anti-lung cancer effects, resulting in a reduction in lung cancer-specific mortality. Furthermore, their superior lipid-lowering abilities may also contribute to more effective mitigation of radiation-induced lung toxicity.

To date, there have been no previous investigations on the relationship between cDDD, DDD, and mortality outcomes in LSCC patients receiving CCRT. The study findings demonstrate a significant correlation between higher cDDD of statin use (**Figure 3**) and greater intensity of daily dose, leading to a lower risk of lung cancer-specific mortality (Supplementary Figures 1, 2; **Tables 2** and **3**). Additionally, the utilization of statins following radiotherapy was associated with a substantial reduction in stroke and epilepsy incidences and showed a trend towards significantly decreasing cardiovascular and cerebrovascular events [19, 49, 50]. These results underscore the importance of appropriate statin dosage during CCRT and in the post-RT period for lung cancer patients, as it plays a critical role in enhancing the anticancer effects of CCRT and mitigating the associated toxici-

ties, ultimately leading to improved overall survival.

Our study possesses several notable strengths. Firstly, it represents a pioneering investigation in exploring the association between cumulative and daily intensity dosages of statins, as well as different statin classes, in relation to the outcomes of unresectable stage III LSCC patients undergoing standard CCRT. This novel approach fills a significant knowledge gap concerning the specific effects of statins on this patient population undergoing CCRT. Secondly, our study implemented a consistent and well-defined treatment protocol for CCRT, utilizing a platinum-based chemotherapy regimen combined with a standard radiation dose. This standardized treatment approach ensures the uniformity and comparability of the study cohort, thereby enhancing the validity of the findings. Thirdly, our study employed the principles of IMRT for radiation treatment. By utilizing IMRT, we ensured optimal treatment accuracy and minimized potential confounding factors associated with variations in radiation therapy techniques [51]. Lastly, our study employed a PSM approach, creating a well-matched cohort to examine the impact of statin use on the survival outcomes of lung cancer patients undergoing CCRT. This methodology helps control for potential confounders and enhances the internal validity of the study, allowing for more reliable and robust conclusions to be drawn.

Several limitations should be acknowledged in this study. Firstly, the assessment of specific toxicity profiles associated with statin use was not feasible, potentially introducing biases into the estimates and affecting the occurrence of statin-related side effects. Nonetheless, efforts were made to minimize confounding by matching patients based on comorbidities, clinical stages according to the AJCC criteria, and considering physical activity levels measured by Eastern Cooperative Oncology Group performance statuses. Secondly, the study population consisted exclusively of Asian patients with LSCC undergoing CCRT, which may limit the generalizability of the findings to other ethnic groups. However, no reports have demonstrated significant variations in gene mutations and outcomes among different ethnic populations with LSCC undergoing CCRT. Thirdly, comorbid conditions were diagnosed based on ICD-9-CM and ICD-10-CM codes, introducing a potential degree of inaccuracy. Nevertheless, the Taiwan Cancer Registry Administration has implemented measures to verify diagnoses through chart reviews and patient interviews, and hospitals found to have discrepancies or engage in malpractice may face penalties. Fourthly, the study sample size is relatively small, but despite this limitation, statistically significant differences in survival outcomes between statin users and non-statin users among lung cancer patients undergoing CCRT were successfully demonstrated. Fifthly, while PSM is commonly employed in observational cohort studies, it may not entirely account for all population differences, leaving room for residual confounding [52]. Lastly, unknown selection biases may exist in the use of statins or non-statin treatments. Therefore, a large-scale randomized trial involving carefully selected patients undergoing appropriate treatments is warranted to provide more definitive conclusions regarding the effectiveness of statin use in treating patients with lung cancer undergoing standard CCRT.

Conclusion

Our study provides compelling evidence supporting the beneficial effects of statin use during the CCRT period, leading to improved overall survival and lung cancer-specific survival rates in patients with unresectable stage III LSCC who undergo definitive CCRT. Pravastatin and fluvastatin exhibited the greatest potential in reducing lung cancer-specific mortality among statins, with rosuvastatin following closely behind. Atorvastatin demonstrated comparable effectiveness, while simvastatin and lovastatin displayed lower efficacy in this regard. Furthermore, our findings establish a clear dose-response relationship, with higher cumulative dose of statin use and greater daily dose intensity associated with reduced lung cancer-specific mortality. These findings highlight the potential of incorporating statin therapy during CCRT to enhance outcomes for patients with advanced lung cancer.

Acknowledgements

Thanks to Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, supports Szu-Yuan Wu's work (Funding Numbers: 10908, 10909, 11001, 11002, 11003, 11006). The data sets support-

ing the study conclusions are included in the manuscript. We used data from the National Health Insurance Research Database and Taiwan Cancer Registry database.

Disclosure of conflict of interest

None.

Abbreviations

LSCC, lung squamous cell carcinoma; CCRT, Concurrent chemoradiotherapy; RT, Radiotherapy; IMRT, Intensity modulated radiation therapy; AJCC, American Joint Committee on Cancer; PSM, Propensity score matching; CI, Confidence interval; aHR, Adjusted hazard ratio; NCCN, National Comprehensive Cancer Network; TCRD, Taiwan Cancer Registry Database; CCI, Charlson comorbidity index; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; HR, hazard ratio; NHIRD, National Health Insurance Research Database; ATC, Anatomical Therapeutic Chemical; cDDDs, cumulative defined daily doses; DDD, defined daily doses; WHO, World Health Organization; RCT, randomized controlled trial.

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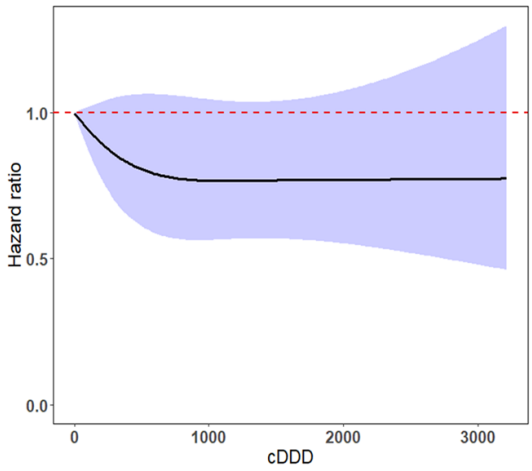
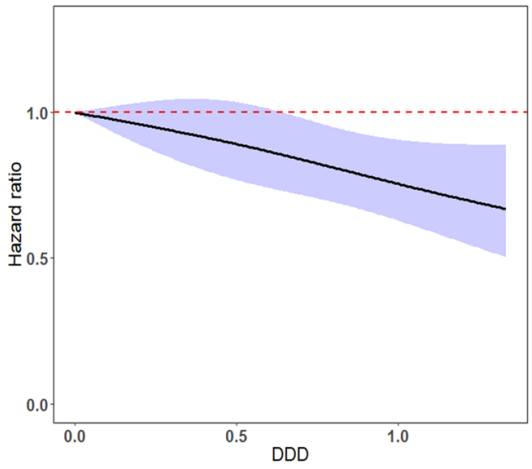
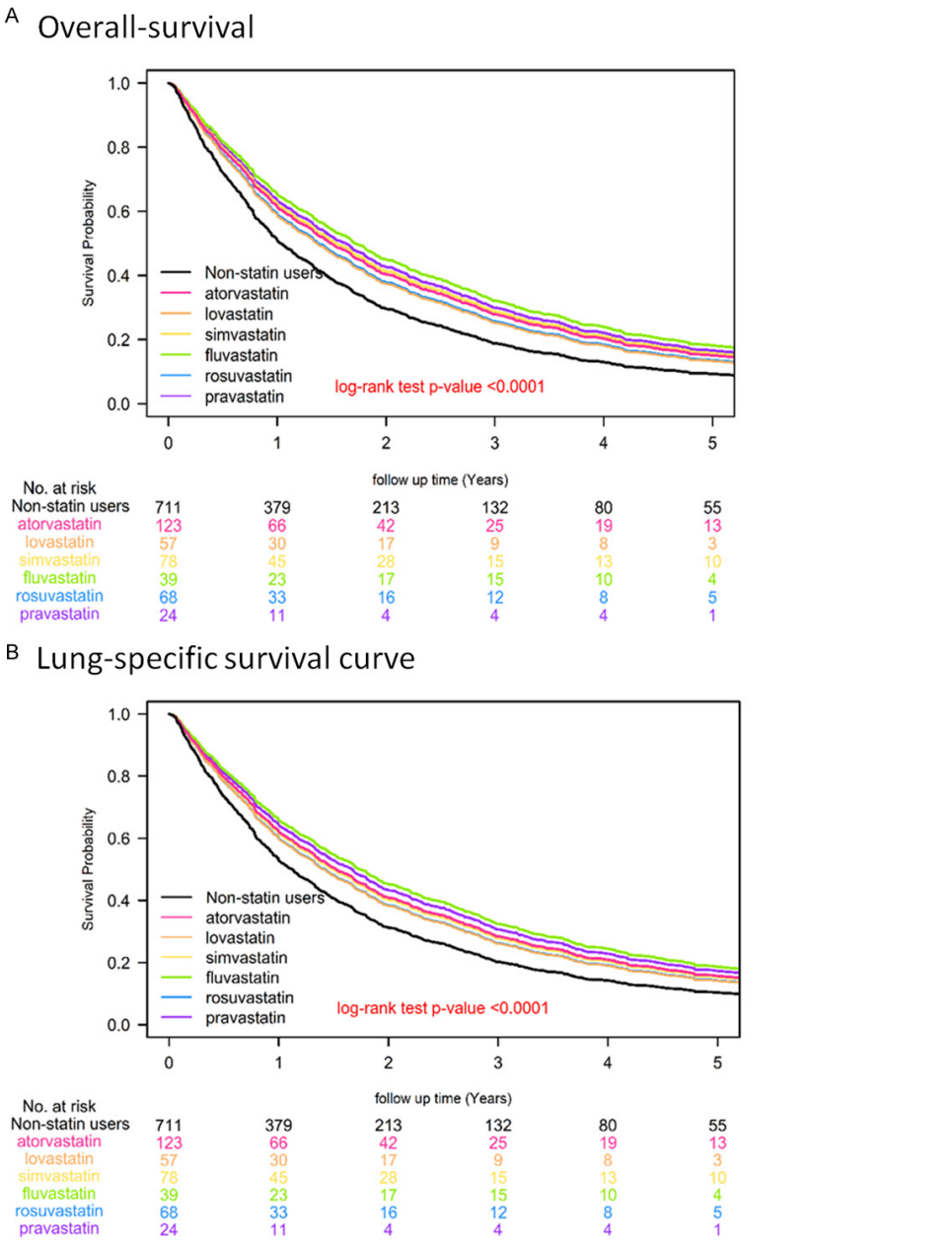


Supplementary Figure 1. The cDDD and the hazard ratio of lung cancer-specific mortality in stage III lung squamous cell carcinoma patients with and without statin use following standard definitive CCRT.



Supplementary Figure 2. Intensity of statin use (DDD) and the hazard ratio of lung cancer-specific mortality in stage III lung squamous cell carcinoma patients with and without statin use following standard definitive CCRT.



Supplementary Figure 3. Kaplan-Meier curves for overall survival and lung cancer-specific survival in stage III lung squamous cell carcinoma patients treated with different types of statins following standard definitive concurrent chemoradiotherapy.