Practical Radiation Oncology® (2021) 11, e459–e467

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Basic Original Report

Statin Use, Heart Radiation Dose, and Survival in Locally Advanced Lung Cancer

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Received 6 October 2020; revised 3 December 2020; accepted 28 December 2020

Abstract

Purpose: Patients with locally advanced non-small cell lung cancer (LA-NSCLC) have a high prevalence of pre-existing coronary heart disease and face excess cardiac risk after thoracic radiation therapy. We sought to assess whether statin therapy is a predictor of overall survival (OS) after thoracic radiation therapy.

Methods and Materials: We performed a retrospective analysis of 748 patients with LA-NSCLC treated with thoracic radiation therapy, using Kaplan-Meier OS estimates and Cox regression.

Results: Statin use among high cardiac risk patients (Framingham risk $\geq$20% or pre-existing coronary heart disease; n = 496) was 51.2%. After adjustment for baseline cardiac risk and other prognostic factors, statin therapy was associated with a significantly increased risk of all-cause mortality (adjusted hazard ratio, 1.39; 95% confidence interval [CI], 1.00-1.91; $P = .048$) but not major adverse cardiac events (adjusted hazard ratio, 1.18; 95% CI, 0.52-2.68; $P = .69$). Among statin-naïve patients, mean heart dose $\geq$10 Gy versus <10 Gy was associated with a significantly increased risk of all-cause mortality (hazard ratio, 1.32; 95% CI, 1.04-1.68; $P = .022$), with 2-year OS estimates of 46.9% versus 60.0%, respectively. However, OS did not differ by heart dose among patients on statin therapy (hazard ratio, 1.00; 95% CI, 0.76-1.32; $P = 1.00$; P-interaction = .031), with 2-year OS estimates of 46.9% versus 50.3%, respectively.

Sources of support: This work had no specific funding.

Disclosures: There are no actual conflicts of interest with this work. Relationships are self-held unless noted otherwise. Dr Bitterman: Agios Pharmaceuticals (consultant). Dr Williams: Varian Medical Systems (research grant to institution). Dr Aerts: Sphera (consultant), Genospace (consultant). Dr Hoffmann: Medimmune (research grant to institution), Kowa Inc. (research grant to institution), and HeartFlow, Inc (research grant to institution). Dr Nohria: Amgen, Inc (research grant to institution), Takeda Oncology (consultant). Dr Mak: AstraZeneca (scientific advisory board), NewRT (honorarium), ViewRay, Inc (medical advisory board; research grant). The remaining authors have nothing to disclose.

Data sharing statement: Research data are not available at this time.

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https://doi.org/10.1016/j.prro.2020.12.006

Conclusions: Among patients with LA-NSCLC, only half of statin-eligible high cardiac risk patients were on statin therapy, reflecting the highest cardiac risk level of our cohort. Statin use was an independent predictor of all-cause mortality but not major adverse cardiac events. Elevated mean heart dose (≥10 Gy) was associated with increased risk of all-cause mortality in statin-naïve patients but not among those on statin therapy, identifying a group of patients in which early intervention with statins may mitigate the deleterious effects of high heart radiation therapy dose. This warrants evaluation in prospective trials.

Introduction

Concurrent chemoradiation therapy, with or without surgery, remains the standard curative treatment of locally advanced non-small cell lung cancer (LA-NSCLC); however, outcomes remain poor, with few long-term survivors.[1-4] Notably, recent clinical trials have observed improved 5-year survival rates of 15% to 20% with median survival times greater than 2 years,[4,5] and promising outcomes have been observed with the addition of consolidative immunotherapy after definitive chemoradiotherapy.[6] Together, these findings have motivated greater understanding of the clinical significance of assessing baseline health risks and treatment-related toxicities as patient outcomes improve.

Patients with lung cancer represent a distinctly high cardiovascular risk group: More than 40% have pre-existing cardiovascular disease (CVD), and the risk of fatal heart disease is significantly elevated even within the first year after diagnosis.[7,8] This excess cancer therapy—related cardiac risk may be partially attributed to thoracic radiation therapy, based on several studies demonstrating the association between cardiac radiation dose exposure and early-onset cardiac events and mortality.[9-11] However, early data have shown that less than half of these patients are on optimal guideline-based medical therapy as recommended by the American Heart Association/American College of Cardiology.[7,12] In addition, shared risk profiles exist between coronary heart disease (CHD) and cancer, and increased cancer-related morbidity and mortality have been observed in patients at high enough baseline cardiac risk to meet eligibility for guideline-based statin therapy.[13,14] Although recent data in lung cancer suggest that statin exposure may improve survival,[15-17] results have been mixed,[18] underscoring the need for further evaluation of the effect of statin exposure on survival in this high-risk population.

The primary objective of the current study was to assess statin use in a large cohort of patients with LA-NSCLC treated with thoracic radiation therapy and ascertain whether statin use at the time of radiation therapy is a predictor of overall survival (OS), adjusting for traditional lung cancer and cardiovascular prognostic factors. This study provides a deeper understanding of the current status of statin use among high cardiac risk patients with lung cancer and provides insight into strategies by which oncologists, primary care physicians, and cardiologists can optimize medical management to mitigate cardiac risk in the setting of cancer therapy.

Methods and Materials

Patient population and treatment

This retrospective cohort study included 748 consecutive patients with clinical stage II (medically inoperable or unresectable) or III LA-NSCLC treated with thoracic radiation therapy at Dana-Farber Cancer Institute/Brigham and Women's Hospital at Milford Regional Medical Center between November 1998 and January 2014. This study was approved by the Dana-Farber/Harvard Cancer Center review board. Patients were treated with a combination of radiation therapy plus chemotherapy and/or surgery. Chemotherapy was most commonly a platinum doublet. Radiation therapy was planned using 3-dimensional conformal radiation therapy or intensity modulated radiation therapy techniques and excluded patients treated with stereotactic body radiation therapy. Cardiac radiation therapy dose exposure was delineated manually as previously described.[9]

Cardiac comorbidities and endpoints

CVD risk factors and post—radiation therapy cardiac events were assessed by in-depth medical record review by a single physician (K.M.A.) with adjudication of clinical criteria by an experienced cardiologist (A.N.) as previously described.[9] Briefly, medical history, medications, vitals, notes (eg, consultation, follow-up, admissions, reports (diagnostic imaging, procedure, electrocardiograms), and laboratory values (eg, cardiac enzymes, lipids) were comprehensively searched via an electronic medical record query tool using standardized search terms and phrases. Pre-existing CHD was defined as a diagnosis of coronary artery disease (CAD), congestive heart failure (CHF), or a CHD risk-equivalent (eg, peripheral vascular disease, stroke). For patients without CHD, the 10-year Framingham CVD risk was calculated using a body mass index—based calculator when pre—radiation therapy lipid levels were unavailable.[19] Statin use was defined as occurring at the time of radiation therapy consultation or prior, based primarily on the medication list as documented in the consultation

note(s) or as a listed prescription in the medical record. High cardiac risk was defined as either high (≥20%) 10-year Framingham risk or pre-existing CHD (or CHD risk-equivalent). Low-to-moderate cardiac risk was defined as <20% 10-year Framingham risk. The endpoint of major adverse cardiac events (MACE)[20] was defined as occurring after day 1 of radiation therapy or ≥30 days post-operatively (when applicable) and included cardiac death, unstable angina, myocardial infarction (MI), heart failure hospitalization or urgent visit, and coronary revascularization. Clinical follow-up included primary, cardiac, and oncologic care; determination of cause of death was previously reported.[9]

Statistical analysis

Descriptive statistics were used to report the distribution of clinical characteristics by statin use status. Continuous covariates were compared using the Wilcoxon rank sum test, and categorical covariates were compared using the Fisher exact test. Kaplan-Meier estimates of OS were calculated and graphically displayed, stratified by statin use and mean heart radiation therapy dose. Survival estimates were compared using log-rank 2-sided P value. Cumulative incidence estimates of MACE accounted for noncardiac death as a competing risk.[21] MACE estimates were compared using a 2-sided Gray's P value. Mortality and MACE estimates were stratified based on mean heart dose ≥10 Gy versus <10 Gy because this cut-point recently demonstrated an association with increased risk of MACE and all-cause mortality.[9]

Cox and Fine and Gray univariable and multivariable regressions[22,23] were performed to determine whether statin use was associated with OS or MACE, respectively, adjusting for lung cancer and CVD prognostic factors and cancer treatment factors. For the models, time 0 was the start date of radiation therapy and concluded by the date of first MACE or death, respectively. Covariables with a $P \leq .05$, in addition to statin use, were included in the model. A 2-sided $P \leq .05$ was considered statistically significant. Stata statistical software (version 15.1; StataCorp LLC, College Station, TX) was used for all analyses.

Results

Clinical characteristics

Patients on statins (n = 305) compared with statin-naïve patients (n = 443) were more likely to be older (median 67 vs 62 years, $P < .001$), have a history of smoking (61.0% vs 46.1%, $P < .001$), hypertension (69.8% vs 36.6%, $P < .001$), hyperlipidemia (85.6% vs 22.1%, $P < .001$), diabetes (24.6% vs 6.8%, $P < .001$), peripheral vascular disease (14.1% vs 4.1%, $P < .001$), stroke (3.6% vs 0.7%, $P = .004$), CAD (44.9% vs 17.8%, $P < .001$), and CHF (14.8% vs 3.6%, $P < .001$) and have higher median Framingham risk (20.8% vs 13.4%, $P < .001$), with no significant difference in sex, performance status, cancer stage, chemotherapy use, radiation therapy technique or prescription dose, or cardiac radiation therapy dose ($P > .05$) (Table 1).

Statin use and cardiac risk

Statin use during radiation therapy by Framingham risk group (low, moderate, or high) or known CHD was 15.7%, 25.8%, 37.2%, and 63.1%, respectively. Indeed, even among statin-eligible high cardiac risk patients (66%, n = 496), defined as those harboring high (≥20%) 10-year Framingham risk or pre-existing CHD, only 51.2% were on a statin at the time of radiation therapy. Furthermore, these high cardiac risk patients on statins (compared with no statin) were similarly more likely to have a history of hypertension (76.3% vs 51.4%, $P < .001$), hyperlipidemia (83.4% vs 29.2%, $P < .001$), diabetes (28.1% vs 11.5%, $P < .001$), former smoking (62.1% vs 49.4%, $P = .017$), peripheral vascular disease (17.1% vs 7.4%, $P = .001$), CAD (54.2% vs 32.5%, $P < .001$), MI (26.1% vs 8.2%, $P = .001$), and CHD (17.8% vs 6.6%, $P < .001$), with no significant difference in age, sex, performance status, cancer stage, chemotherapy use, radiation therapy prescription dose, or cardiac radiation therapy dose exposure ($P > .05$) (Table E1).

OS analysis

The median follow-up was 20.4 months (interquartile range [IQR], 8.4-45.0 months) overall and 48.1 months (IQR, 31.6-76.4 months) in patients who were still alive. A total of 533 patients died (71.3%); the majority of deaths were lung cancer related (n = 357, 67.0%), and 27 (5.1%) were from cardiac causes, 41 (7.7%) were from known noncardiac causes, and 108 (20.3%) were from unknown causes. Among the 533 deaths, 309 of 443 (69.8%) versus 224 of 305 (73.4%) occurred in patients not taking versus taking a statin, respectively. The median OS for the total population was 22.3 months (IQR, 9.8-45.7 months). On univariate analysis, there was a trend toward increased risk of all-cause mortality in patients on statin therapy (unadjusted hazard ratio [HR], 1.18; 95% confidence interval [CI], 0.99-1.40; $P = .062$), with 2-year OS estimates of 53.3% (95% CI, 48.5-57.9) versus 48.0% (95% CI, 42.2-53.5), respectively (Fig 1A).

After adjustment for age, sex, performance status, unintentional weight loss, nodal stage, CVD factors (stroke, peripheral vascular disease, MI, CHF, arrhythmia, high Framingham risk or known CHD), treatment regimen, radiation therapy year, and mean heart radiation

Table 1 Patient and treatment characteristics

Characteristic	No statin (n = 443)	Statin (n = 305)	*P*
Age, median (IQR) y	62 (55, 71)	67 (61, 75)	<.001
Sex,			
Female	229 (51.7%)	139 (45.6%)	.058
Male	214 (48.3%)	166 (54.4%)	
ECOG performance status			
0-1	396 (89.4%)	264 (86.6%)	.39
2	38 (8.6%)	31 (10.2%)	
3-4	9 (2.0%)	10 (3.9%)	
Weight loss	144 (32.5%)	93 (30.5%)	.31
Tobacco use			
Never	44 (9.9%)	16 (5.3%)	<.001
Current	195 (44.0%)	103 (33.8%)	
Former	204 (46.1%)	186 (61.0%)	
Pack-years, median (IQR)	40 (30, 60)	45 (30, 70)	.09
Medical comorbidities			
Hypertension	162 (36.6%)	213 (69.8%)	<.001
Hyperlipidemia	98 (22.1%)	261 (85.6%)	<.001
Diabetes mellitus	30 (6.8%)	75 (24.6%)	<.001
DVT/PE	19 (4.3%)	51 (4.9%)	.41
Arrhythmia	52 (11.7%)	51 (16.7%)	.034
Valvulopathy	20 (4.5%)	22 (7.2%)	.080
Peripheral vascular disease	18 (4.1%)	43 (14.1%)	<.001
Stroke	3 (0.7%)	11 (3.6%)	.004
Coronary artery disease	79 (17.8%)	137 (44.9%)	<.001
Myocardial infarction	20 (4.5%)	66 (21.6%)	.001
Congestive heart failure	16 (3.6%)	45 (14.8%)	<.001
Framingham risk			
Median (IQR), %	13.4 (7.5, 23.8)	20.8 (11.2, 34.8)	<.001
Low (<10%)	113 (32.9%)	21 (15.4%)	<.001
Moderate (10%-20%)	89 (25.9%)	31 (22.8%)	
High (>20%)	142 (41.3%)	84 (61.8%)	
NSCLC clinical overall stage			
II	43 (9.7%)	36 (11.8%)	.62
IIIA	252 (56.9%)	166 (54.4%)	
IIIB	148 (33.4%)	103 (33.8%)	
NSCLC clinical nodal stage			
N0-1	113 (25.6%)	76 (24.9%)	.86
N2-3	329 (74.4%)	229 (75.1%)	
Tumor laterality			
Right	249 (59.7%)	168 (59.8%)	1.0
Left	168 (40.3%)	113 (40.2%)	
NSCLC histology			
Adenocarcinoma	189 (42.7%)	142 (46.6%)	.61
Squamous cell carcinoma	139 (31.4%)	95 (31.2%)	
Other	115 (26.0%)	68 (22.3%)	
Chemotherapy type			
Induction	100 (22.6%)	58 (19.0%)	.274
Concurrent	383 (86.5%)	258 (84.5%)	.524
Adjuvant	153 (34.5%)	94 (30.8%)	.304
RT/surgery sequence			
Definitive chemo-RT	249 (56.2%)	184 (60.3%)	.054
Preoperative RT/chemo-RT	116 (26.2%)	55 (18.0%)	
Postoperative RT/chemo-RT	46 (11.1%)	39 (12.8%)	
RT alone	29 (6.6%)	27 (8.9%)	
RT technique			
3D-CRT	355 (80.1%)	229 (75.1%)	.106

(*continued on next page*)

Table 1 (*continued*)

Characteristic	No statin (n = 443)	Statin (n = 305)	*P*
IMRT	88 (19.9%)	76 (24.9%)	
RT year			
<2008	177 (40.0%)	96 (31.5%)	.020
≥2008	266 (60.1%)	209 (68.5%)	
RT dose, Gy			
Prescribed RT dose, median (IQR)	64 (54, 66)	64 (56, 66)	.763
Mean whole heart dose, median	11.6 (5.8, 19.1)	12.9 (6.3, 18.9)	.498
Mean LAD dose, median	7.1 (2.0, 17.6)	8.1 (2.5, 18.2)	.233
Mean lung dose, median	14.9 (11.5, 17.1)	14.9 (11.6, 17.5)	.205

Abbreviations: 3D-CRT = 3D-conformal radiation therapy; chemoRT = chemoradiotherapy; DVT = deep venous thrombosis; ECOG = Eastern Cooperative Oncology Group; IMRT = intensity modulated radiation therapy; IQR = interquartile range; LAD = left anterior descending coronary artery; NSCLC = non-small cell lung cancer; PE = pulmonary embolism; RT = radiation therapy.
Values are n (%) unless otherwise specified. The distributions of categorical covariates were compared using the Fisher exact test, while continuous variables were compared using the Wilcoxon rank sum test.

therapy dose exposure, a significant increase in the risk of all-cause mortality was observed in patients on statin therapy (adjusted hazard ratio [AHR], 1.39; 95% CI, 1.00-1.91; $P = .048$) (Table 2). Furthermore, a significant interaction was observed between statin use and mean heart dose (AHR, 0.98; 95% CI, 0.96-1.00; $P = .031$). Specifically, for the 443 patients not on statin therapy, treatment with mean heart dose ≥10 Gy versus <10 Gy was associated with a significantly higher risk of all-cause mortality (164 vs 116 deaths; HR, 1.32; 95% CI, 1.04-1.68; $P = .022$), with 2-year OS estimates of 46.9% (95% CI, 40.2%-53.3%) versus 60.0% (95% CI, 52.4-66.8%), respectively (Fig 1B). Among the 305 patients on statin therapy, there was no observed increased risk of all-cause mortality with mean heart dose ≥10 Gy versus <10 Gy (126 vs 84 deaths; HR, 1.00; 95% CI, 0.76-1.32; $P = 1.00$), with 2-year OS estimates of 46.9% (95% CI, 39.3%-54.1%) versus 50.3 (95% CI, 40.7%-59.1%), respectively (Fig 1C).

Similarly, among Framingham low-to-moderate-risk patients (Framingham risk <20%), after adjustment for age, sex, performance status, unintentional weight loss, nodal stage, Framingham risk, treatment regimen, radiation therapy year, and mean heart radiation therapy dose exposure, a significant increase in the risk of all-cause mortality was observed in patients on statin therapy (AHR, 3.54; 95% CI, 1.72-7.27; $P = .001$), and a significant interaction was observed between statin use and mean heart dose (AHR, 0.94; 95% CI, 0.90-0.98; $P = .007$) (Table E2). Specifically, for the 181 statin-naïve patients with Framingham risk <20%, treatment with mean heart dose ≥10 Gy versus <10 Gy was associated with a significantly higher risk of all-cause mortality (64 vs 46 deaths; HR, 1.49; 95% CI, 1.02-2.19; $P = .039$), with 2-year OS estimates of 50.2% (95% CI, 39.7%-59.8%) versus 70.7% (95% CI, 59.6%-79.3%), respectively (Fig E1B). Among the 49 patients with Framingham risk <20% on statin therapy, there was no observed increased risk of all-cause mortality with mean heart dose ≥10 Gy versus <10 Gy (19 vs 16 deaths; HR, 0.56; 95% CI, 0.29-1.43; $P = .11$), with 2-year OS estimates of 67.7% (95% CI, 48.4%-81.2%) versus 44.4% (95% CI, 21.6%-65.1%), respectively (Fig E1C).

MACE analysis

Of 748 patients, 77 (10.3%) developed ≥1 MACE. The median time to first MACE was 18.5 months (IQR, 5.4-33.6 months). Consistent with the elevated baseline cardiac risk in patients on statin therapy versus statin-naïve patients (Table 1, Table E1), there was an increased risk of MACE in patients on statin therapy (versus statin naïve) (45 vs 32 patients with ≥1 MACE; unadjusted HR, 2.16; 95% CI, 1.37-3.39; $P = .001$), with 2-year cumulative incidence estimates of 9.0% (95% CI, 6.1%-12.6%) versus 3.6 (95% CI, 2.2%-5.7%), respectively. However, after adjustment for age, hypertension, diabetes, stroke, peripheral vascular disease, CAD, CHF, arrhythmia, high Framingham risk or known CHD, or type of radiation therapy, there was no longer a significantly elevated risk of MACE associated with statin therapy (AHR,1.18; 95% CI, 0.52-2.68; $P = .69$) (Table E3). Among Framingham low-to-moderate-risk patients (Framingham risk <20%), there was a significant interaction between statin therapy and mean heart radiation therapy dose (HR, 1.14; 95% CI, 1.01-1.28; $P = .038$), but no statistically significant difference in the risk of MACE with statin therapy (MACE n = 11; HR, 0.08; 95% CI, 0.00-5.46; $P = .24$) in the setting of limited events observed in this lower risk cohort.

Discussion

Among our large cohort of patients with LA-NSCLC, only half of statin-eligible high cardiac risk patients were on statin therapy at the time of radiation therapy. Even

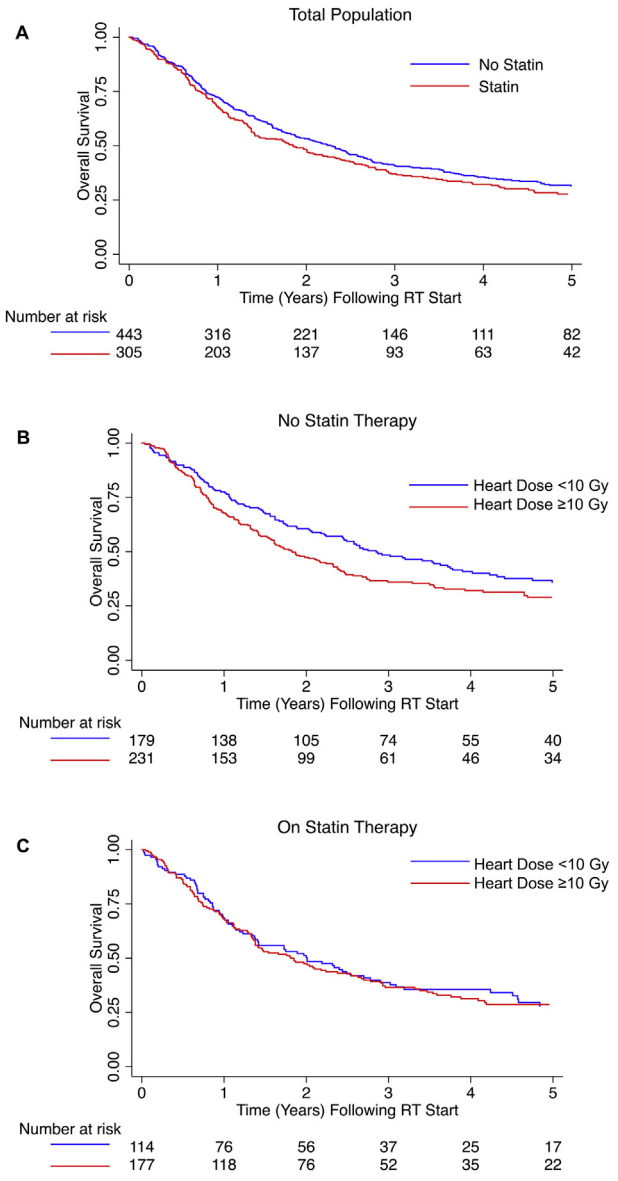

Figure 1 Overall survival estimates stratified by (A) statin use (log-rank $P = .061$) or mean heart dose <10 Gy versus ≥10 Gy in (B) patients not on statin therapy (log-rank $P = .022$) and (C) patients on statin therapy (log-rank $P = .997$). *Abbreviation:* RT = radiation therapy.

among high cardiac risk patients, those on statin therapy harbored significantly more cardiac risk factors than those not on statins, suggesting only those of highest cardiac risk were on lipid-lowering therapy at the time of radiation therapy. Statin use was a significant independent predictor of all-cause mortality but not MACE, and there was a significant interaction between statin use and mean heart radiation therapy dose; among statin-naïve patients, mean heart dose ≥10 Gy versus <10 Gy was associated with a significantly increased risk of all-cause mortality, with 2-year OS estimates of 46.9% versus 60.0%, respectively, whereas there was no significant difference among patients on statin therapy. These findings were similarly observed among statin-naïve patients with Framingham risk <20%, with 2-year OS estimates of 50.2% versus 70.7% with mean heart dose ≥10 Gy versus <10 Gy, respectively. Together, these results demonstrate that only the highest cardiovascular risk patients were on statin therapy during cancer treatment, and these patients harbor increased risk of mortality despite statin therapy. Furthermore, we identify a subgroup of high cardiac risk patients (statin naïve, high heart radiation therapy dose) for whom prospective study of more aggressive cardiac risk mitigation strategies such as statin intervention may be warranted.

Although prior population-based studies have detailed statin use among patients with various types of cancer (including lung cancer subsets), these studies did not account for cancer stage, treatment factors, or assessment of baseline cardiac risk.[7,17,24,25] Notably, Al-Kindi and Oliveira[7] reported that among patients with cancer and known CVD, only half were treated with guideline-based medical therapy or were referred for cardiology consultation at the time of their cancer diagnosis. Our data are consistent with these findings, in that only half of statin-eligible high cardiac risk patients with LA-NSCLC were on statin therapy at the time of radiation therapy. Moreover, we observed that patients on statin therapy reflected the highest cardiac risk level of our cohort; even among high cardiac risk patients, those on statin therapy harbored significantly more cardiac risk factors than statin-naïve patients and had increased risk of MACE. Together, these findings underscore the importance of detailed cardiac risk assessment and medical optimization in patients with LA-NSCLC.

The significant interaction we observed between mean heart radiation therapy dose and statin use is consistent with the overall lower cardiac risk of statin-naïve patients versus those on statin therapy, as well as our recent report demonstrating a significant interaction between heart radiation therapy dose and baseline CHD, such that the increased risk of MACE and all-cause mortality with increasing heart radiation therapy dose is most prominent in CHD-negative patients.[9] The etiology of these differences is not clear, but possible contributing pathophysiologic factors include differential susceptibility to radiation-mediated microvascular disease and/or myocardial fibrosis, depending on the extent and distribution of pre-existing coronary obstructive patterns.[26-28] Importantly, this is not to suggest that heart radiation therapy dose is not meaningful in high cardiac risk patients (eg, on statin therapy or with known CHD), but we hypothesize that these findings are due to exceeding an observable radiation dose-response relationship in these ultrahigh cardiac risk patients, given their high rates of MACE and mortality.[9] Rather, we posit that much lower cardiac radiation therapy dose limits and more aggressive risk mitigation strategies, such as cardiac medication

Table 2 Cox regression analysis for all-cause mortality

Covariable	No. of patients	No. of ACD	Univariable		Multivariable	
			HR (95% CI)	*P*	AHR (95% CI)	*P*
Lung cancer factors						
Age (year)*	748	533	1.02 (1.01-1.03)	<.001	1.00 (.99-1.01)	.77
Sex*						
Female	368	251	1.00 (referent)		1.00 (referent)	
Male	380	282	1.20 (1.01-1.43)	.034	1.09 (.90-1.33)	.37
ECOG performance status						
0-1	660	458	1.00 (referent)		1.00 (referent)	
2-4	88	75	1.63 (1.28-2.09)	<.001	1.56 (1.19-2.03)	.001
Smoking*						
Never	60	40	1.00 (referent)			
Current	298	213	1.29 (0.92-1.82)	.14		
Former	390	280	1.30 (0.93-1.81)	.12		
Weight loss	237	173	1.33 (1.10-1.59)	.002	1.24 (1.02-1.50)	.032
Overall stage						
II	79	53	1.00 (referent)			
III	669	480	1.18 (.89-1.57)	.25		
Nodal stage						
0-1	189	123	1.00 (referent)		1.00 (referent)	
≥2	558	410	1.25 (1.02-1.53)	.032	1.21 (.98-1.50)	.077
Tumor laterality						
Right	417	300	1.00 (referent)			
Left	281	200	0.97 (.81-1.16)	.71		
Histology						
Adenocarcinoma	331	232	1.00 (referent)			
Nonadenocarcinoma	417	301	1.17 (.99-1.39)	.065		
Baseline cardiac factors						
Hypertension	375	272	1.07 (.91-1.27)	.41		
Hyperlipidemia	359	259	1.07 (.90-1.26)	.46		
Diabetes	105	80	1.11 (.87-1.40)	.40		
Stroke	14	12	2.00 (1.13-3.55)	.018	1.26 (.67-2.35)	.47
Peripheral vascular disease	61	52	1.45 (1.09-1.93)	.011	1.03 (.75-1.42)	.85
Coronary artery disease	216	162	1.14 (.95-1.37)	.17		
Myocardial infarction	86	72	1.47 (1.15-1.88)	.002	1.22 (.91-1.63)	.18
Congestive heart failure	61	50	1.34 (1.00-1.79)	.052	.89 (.64-1.24)	.49
Arrhythmia	103	80	1.36 (1.08-1.73)	.011	1.28 (0.99-1.65)	.063
Valvulopathy	42	32	1.37 (.96-1.96)	.087		
High Framingham or CHD	496	369	1.46 (1.22-1.76)	<.001	1.14 (.89-1.46)	.30
On statin	305	224	1.18 (.99-1.40)	.062	1.39 (1.00-1.91)	.048
Treatment sequence						
Definitive RT/chemoRT	489	398	1.00 (referent)			
Neoadj./adj. RT/chemoRT	259	135	.40 (.33-.48)	<.001	.42 (.34-.52)	<.001
Chemotherapy (any)	706	501	.75 (.52-1.07)	.114		
RT treatment factors						
Technique						
3D-CRT	584	423	1.00 (referent)			
IMRT	164	110	1.14 (.92-1.40)	.23		
RT year						
<2008	273	235	1.00 (referent)		1.00 (referent)	
≥2008	475	298	.83 (.70-.99)	.042	.80 (.66-.97)	.020
Heart RT dose, mean (Gy)	701	490	1.01 (1.00-1.02)	.015	1.02 (1.01-1.03)	.004
Interaction†						
Statin × heart mean RT dose	701	490	.99 (.97-1.00)	.107	.98 (.96-1.00)	.031

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; ACD = all-cause death; AHR = adjusted hazard ratio; CHD = coronary heart disease; chemoRT = chemoradiotherapy; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IMRT = intensity modulated radiation therapy; RT = radiation therapy.

* Both a lung cancer and cardiac prognostic factor.

† Interaction term between statin use (categorical variable) and mean heart RT dose (continuous variable).

optimization, are likely warranted in these patients,[9] although this remains an active area of investigation.

Although an early meta-analysis failed to observe a survival benefit of statin exposure in lung cancer,[24] a survival benefit was observed in patients with lung cancer of all stages in a Danish observational study[25] and a population-based cohort study from the United Kingdom.[17] Although the latter did not account for cancer stage, a recent Surveillance, Epidemiology, and End Results-Medicare analysis in patients with stage IV NSCLC revealed that statin exposure before diagnosis was associated with improved survival.[15] Moreover, a randomized phase 2 study of patients with advanced NSCLC demonstrated a longer progression-free survival with simvastatin treatment in the wild-type epidermal growth factor receptor non-adenocarcinoma subgroup, although statin therapy failed to improve OS.[18] By comparison, we observed that in patients with LA-NSCLC, only the highest cardiovascular risk patients were on statin therapy during cancer treatment, and these patients harbored increased risk of mortality despite statin therapy. Together, these results underscore the importance of prospective evaluation of statin therapy on survival in patients with LA-NSCLC, including comprehensive detailing of baseline cardiovascular risk and heart radiation therapy dose.

This manuscript represents the first series to report statin use by baseline cardiac risk status in patients with LA-NSCLC, accounting for excess cardiac risk due to thoracic radiation therapy. Potential limitations include its retrospective nature, with the risk of selection bias and confounding, because underlying differences in patient characteristics (from both measured and unmeasured variables) may have influenced statin therapy use, cardiovascular medication management, and risk-reducing measures. Therefore, given the marked covariate imbalance and potential magnitude of unmatched patients reducing precision, we employed conventional covariate adjustment without propensity score adjustment.[29] We do not have information regarding the duration of statin use or adherence, lipid levels among all patients to assess goals of statin therapy, or whether patients received guideline-based optimization of other cardiovascular risk factors. Additionally, the median follow-up and survival were less than 2 years in this cohort, limiting long-term cardiac assessment and reflecting the overall poor prognosis, respectively. Lastly, despite in-depth record review, the nature of a large tertiary referral center may underrepresent cardiac risk in these patients because outside medical records reflecting cardiac events may not have been accounted for.

Conclusions

We observed that only half of statin-eligible, high cardiac risk patients with LA-NSCLC were on statin therapy at the time of radiation therapy, illustrating the lack of cardiovascular risk optimization in a large number of eligible patients. Among statin-naïve patients, high mean heart dose was associated with a significantly increased risk of all-cause mortality, whereas there was no significant difference among patients on statin therapy. Based on these findings, we recommend that patients with LA-NSCLC have baseline cardiovascular risk assessed and appropriate American Heart Association/American College of Cardiology guideline-based primary and secondary prevention measures (eg, statin therapy) initiated.[30,31] We hypothesize that in particularly high cardiac risk patients (eg, Framingham risk $\geq$20% or known CHD), much lower cardiac radiation therapy dose limits are likely warranted,[9] although this remains an area of active inquiry. Importantly, the overall implications of statin therapy on mortality in LA-NSCLC warrants prospective evaluation with comprehensive detailing of baseline cardiac risk and heart radiation therapy dose exposure.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.prro.2020.12.006.

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