Original Article
Middle East Journal of Cancer; April 2024; 15(2): 117-127

The Role of Lovastatin in Curative Chemoradiotherapy for Patients with Head and Neck Cancer: A Randomized Trial

Azadeh Sharifian♦, MD, Ehsan Karbasi, MD, Ali Kazemian, MD, Forouzan Nourbakhsh, MD, Reza Nazari, MD, Mahdi Aghili, MD

Radiation Oncology Research Center, Cancer Research Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

Please cite this article as: Sharifian A, Karbasi E, Kazemian A, Nourbakhsh F, Nazari R, Aghili M. The role of lovastatin in curative chemoradiotherapy for patients with head and neck cancer: a randomized trial. Middle East J Cancer. 2024;15(2):117-27. doi:10.30476/mejc.2023.97387.1911.

♦Corresponding Author:
Azadeh Sharifian, MD
Radiation Oncology Research Center, Cancer Research Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
Tel: 021 61192567
Fax: 66948672
Email:azadehsharifian68@gmail.com

Abstract

Background: Evidence suggests that statins can improve survival outcomes and ameliorate treatment-related side-effects in certain malignancies. Statins exhibit various mechanisms of action, including apoptosis induction, proliferation inhibition, tumor radiosensitization, lipid production suppression, and anti-inflammatory effects. This trial aimed to assess the impact of lovastatin on patients with locally advanced head and neck squamous cell carcinoma (HNSCC) undergoing definitive chemoradiation.

Method: In this double-blinded randomized phase 2 clinical trial, 35 patients were randomly allocated to receive either 80 mg of lovastatin daily in conjunction with chemoradiotherapy (case group, n=18) or a placebo (control group, n=17). Primary outcomes included the response rate (RR) after three months, the occurrence of acute and late side-effects, median progression-free survival (PFS), and overall survival (OS).

Results: The complete RR was slightly higher in the statin group (83.3% vs. 64.7%), although it did not reach statistical significance ($P = 0.592$). Acute adverse events did not significantly differ between the two groups. Grade 3 dermatitis occurred more frequently in the placebo group (35.3% vs. 11.1%), while grade 3 mucositis was more common in the statin group (38.9% vs. 11.8%). The median OS was 22 months (confidence interval (CI) 95% = 6.3-37.6) in the statin group and 17 months (CI 95% = 4.9-29.1) in the control group ($P = 0.50$). Median PFS was 20 months (CI 95% = 15.8-24.1) in the statin group and 15 months (CI 95% = 8.2-21.7) in the control group ($P = 0.609$).

Conclusion: Combining lovastatin with chemoradiation augments the therapeutic effect in HNSCC. Larger-scale studies incorporating advanced radiotherapy techniques and baseline lipid profile assessments are necessary to investigate statins' efficacy in HNSCC further.

Keywords: Head and neck neoplasms, Squamous cell carcinoma, Statin, Chemoradiotherapy

Received: April 19, 2023; Accepted: December 04, 2023

Introduction

Head and neck squamous cell carcinomas (HNSCCs) are among the most common cancers (4% of all cancers), and about 60% of HNSCCs are locally advanced at presentation.[1,2] The treatment choice for these cancers is surgical resection in resectable disease and adjuvant radiotherapy. Concurrent chemoradiotherapy (CRT) is recommended as a definitive treatment for unresectable locally advanced head and neck cancer (LAHNC). Chemotherapy administered concurrently as a radiosensitizer has improved survival in this group of patients; however, the prognosis of such patients is still poor.[1] Consequently, other agents with potential anticancer and radio-sensitizing effects might improve outcomes.[3]

Lipids are one of the basic structures of cell membranes and contribute to cell metabolism, including protein synthesis, cell signaling, energy storage, proliferation, differentiation, and apoptosis.[4, 5] Statins inhibit lipid metabolism by blocking the activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA), a key enzyme involved in the regulation of signaling proteins called guanosine diphosphate (GTPase) superfamily, which contribute to tumorigenesis, proliferation, and survival of tumor cells.[5-7] In vivo, studies have shown that statins have anti-proliferative and radiosensitizing effects,[3] and they increase sensitization to radiation by stopping the cell cycle in the late G1 phase.[6] In vivo, studies have demonstrated the apoptotic effects of lovastatin in HNSCC and cervical squamous cell carcinoma (SCC).[8, 9]

Several studies have demonstrated the potential oncologic benefits of statins for some cancers, such as colorectal, prostate, and breast cancers.[10] In a cohort study performed on HNSCC patients, those with hyperlipidemia who received statins showed improvement in overall survival (OS) and disease-specific survival (DSS), compared with the other two groups, including those without hyperlipidemia who used statins and those who neither had hyperlipidemia nor used statins.[11] Another retrospective study conducted on human papillomavirus (HPV)-negative HNSCC showed improvement in OS and DSS in patients who have used statin at least 1 month before and 4 months after diagnosis, compared with non-exposed statin patients.[12]

Most of the studies in the literature have been retrospective cohort trials. Additionally, the number of trials conducted on head and neck cancers in this regard is relatively limited. Consequently, a randomized clinical trial was undertaken to evaluate the effect of lovastatin on the response rate (RR) and complications in patients with locally advanced HNSCC who underwent radiotherapy.

Materials and Methods

Study design and target group

This double-blinded randomized clinical trial was conducted on patients with locally advanced HNSCC referred to the Cancer Institute of Tehran University of Medical Sciences, Tehran, Iran, between 2012 and 2013. The patients were undergoing either definitive CRT due to unresectable tumors or organ preservation.

Inclusion and exclusion criteria

Patients diagnosed with newly detected locally advanced HNSCC (T2-4, N0-3), as per the tumor staging criteria outlined in the American Joint Committee on Cancer (AJCC) 8th edition of 2010, originating from the larynx, base of the tongue, and hypopharynx, and confirmed through biopsy, were enrolled for definitive CRT. They were then randomly assigned into two groups using the permuted block technique (block size = 4). All patients underwent a comprehensive physical examination, and their medical histories were documented. Patients without distant metastasis and displaying average complete blood count (CBC), liver function tests (LFT), and renal function tests (RFT) results were eligible for inclusion in the study. Patients with metastasis or those requiring medications with potential interactions with lovastatin were excluded from the trial.

Treatment protocol

All patients received conventional radiation therapy with a dose of 2 Gy per fraction and three-dimensional conformal radiotherapy. The

Table 1. Comparison of patient groups: age, gender, tumor site, AJCC 8th edition staging, chemotherapy protocol, treatment duration

	Statin group (n=18)	Placebo group (n=17)	*P* value
Mean age	57.9	57.2	0.235
Gender			
Male	84.2%	88.9%	0.677
Female	15.8%	11.1%	
Primary tumor site			
Oral cavity	10.5%	11.1%	0.997
Larynx	84.2%	83.3%	
Hypopharynx	5.3%	5.6%	
Staging			
T4	31.6%	33.3%	0.137
T3	63.2%	66.7%	
T2	5.3%		
N0	26.3%	33.3%	0.137
N1	21.1%	38.9%	
N2	15.8%	22.2%	
N3	36.8%	5.6%	
Chemotherapy protocol			
3-week chemotherapy		16.7%	0.195
Weekly chemotherapy	100%	83.3%	0.195
Duration of treatment			
7 weeks	82%	66%	0.333
7-8 weeks	12%	28%	
More than 8 weeks	6%	6%	

AJCC: American Joint Committee on Cancer

total radiation dose administered to the gross target volume was 70 Gy, and 44-46 Gy was delivered to the subclinical target volume over 7 weeks, with treatment sessions held 5 days per week. Chemotherapy consisted of cisplatin at a dose of 35 mg/m^2, administered weekly or every 3 weeks (35 mg/m^2 on days 1-3) depending on patients' compliance. Additionally, the intervention group was prescribed 80 mg of lovastatin daily, divided into four doses, on days when patients underwent radiotherapy. In contrast, the control group received a placebo for the same duration.

Treatment evaluation

The primary outcome of this study involved evaluating RR through imaging after three months of treatment. Additionally, acute and late side-effects, median progression-free survival (PFS), and OS were assessed in both groups.

Acute reactions were monitored weekly through physical examinations, specifically evaluating mucositis using the World Health Organization (WHO) scoring system and assessing esophagitis and dermatitis based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 scoring system, all performed by the same physician. The highest grade observed during treatment was recorded as the patient's adverse events. Furthermore, routine tests, including CBC, blood urea nitrogen, and creatinine tests, were conducted weekly for all patients. LFT was only required, if patients reported unexplained muscular pain.

Response evaluation was carried out after three months of completing treatment using computed tomography (CT) scans or magnetic resonance imaging (MRI) in conjunction with physical examinations. This assessment involved comparing the pretreatment tumor volume, following the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, to determine the RR in both patient groups.

During the follow-up period, which included history-taking and physical examinations, patients were seen every two months for the initial two years and, subsequently, every six months for five years. Any suspicious local recurrence or distant metastasis cases were confirmed through further diagnostic procedures such as CT scans, MRIs, or biopsies.

Statistical analysis

The formula for comparing the equality of two proportions was applied to determine the sample

Table 2. Treatment complications: Acute reactions (mucositis, esophagitis, dermatitis) graded according to CTCAE v4.0, hematologic complications (Weekly CBC) graded using the WHO system

Complications	Statin group (n=18)	Placebo group (n=17)	*P* value
Mucositis			
G1	11.1%	76.5%	0.176
G2	50%	11.8%	
G3	38.9%	11.8%	
Dermatitis			
G1	38.9%	17.65	0.163
G2	50.2%	47.1%	
G3	11.1%	35.3%	
Dysphagia			
G0	5%	18.1%	0.199
G1	55%	44.4%	
G2	28%	24.4%	
G3	12%	13.3%	
Anemia			
G0	56.3%	70.6%	0.135
G1	43.8%	17.6%	
G2	11.8%	11.8%	
Leukopenia			
G0	38.9%	47.1%	0.866
G1	50%	41.2%	
G2	11.1%	11.8%	
Thrombocytopenia			
G0	27.8%	17.6%	0.767
G1	44.4%	52.9%	
G2	17.8%	29.4%	

CTCAE: Common Terminology Criteria for Adverse Events; CBC: Complete blood count; G0: Grade 0; G1: Grade 1; G2: Grade 2; G3: Grade 3

size. The used significance level (alpha) was 0.05, and the desired statistical power was 80%.

Following prior research findings, the RR associated with definitive chemoradiation was estimated at approximately 65%. Our objective was to enhance this rate to 85% by administering statins. Consequently, our initial target sample size was 70 individuals for each experimental and control group. However, due to a slower-than-anticipated rate of subject enrollment, recruitment was halted after enlisting 35 participants, and an interim analysis was conducted.

The data collected underwent thorough analysis utilizing the Statistical Package for the Social Sciences (SPSS), specifically, Version 21 for Windows (SPSS Inc; Chicago, IL, USA). A $P < 0.05$ was regarded as indicative of statistical significance in all statistical tests conducted.

Kaplan-Meier survival analysis was utilized to estimate actuarial OS and PFS. OS was defined as the duration between the randomization point and the last follow-up or censoring event. Similarly, PFS was defined as the duration between the randomization point and the occurrence of recurrence, the last uneventful follow-up, death, or censoring. The Cox hazards test was also employed to identify factors predictive of OS and PFS.

Ethical considerations

This study was conducted conclusively with the World Medical Association Declaration of Helsinki and approved by the Ethics Committee of Tehran University of Medical Sciences (ethics code: 91/D/130/1291). The trial is registered on IRCT (IRCT 2014121920368N1). The goals of the study were explained to the participants. Then, the patients signed informed consent and were assured that their data would remain confidential to the research team.

Results

In this study, due to the prolonged rate of patient enrollment, 35 patients were randomized

Table 3. Radiologic response and survival rates: 2-year and 5-year events. Details: patient outcomes (no recurrence, locoregional recurrence, death, bone metastasis), 2-year and 5-year survival and PFS medians and percentages

	Statin group	Placebo group	*P* Value
Partial response	16.7%	35.3%	0.592
Complete response	83.3%	64.7%	
Median OS	22m (CI95%=6.3-37.6)	17m (CI95%=4.9-29.1)	0.5
Median PFS	20m (CI95%=15.8-24.1)	15m (CI95%=8.2-21.7)	0.609
Mean OS	30m (CI95%=20.9-40.3)	26m (CI95%=16.3-35.8)	0.5
Mean PFS	27.6m (CI95%=18.2-37)	22.7m (CI95%=13.1-32.7)	0.609
2-year events			0.87
No recurrence	33.3%	23.5%	
LTF	16.6%	23.5%	
Alive LRR	5.5%	5.8%	
Death met	11.1%	17.6%	
Death LRR	16.6%	17.6%	
Alive bone metastasis	11.1%	5.8%	
Death infection	5.5%	0.0%	
Death MI	0.0%	5.8%	
2y OS	49% (CI95%=26-72)	41% (CI95%=18-64)	
2y PFS	33% (CI95%=14-52)	24% (CI95%=5-43)	
5-year events			
Previously death	33.3%	35.2%	0.82
LFT	33.3%	29.4%	
Alive LRR	0.0%	5.8%	
No recurrence	11.1%	5.8%	
Death LRR	5.5%	5.8%	
Death due to metastasis	5.5%	17.6%	
Death stroke	5.5%	0.0%	
Death MI	5.5%	0.0%	
5y OS	25% (CI95%=4-46)	18% (CI95%=0-37)	
5y PFS	17% (CI95%=0-34)	18% (CI95%=0-37)	

LTF: Lost to follow-up; LRR: Locoregional recurrence; OS: Overall survival; PFS: Progression - free survival; CI: Confidence interval; MI: Myocardial infarction

into two groups: the intervention group (n=18) and the placebo group (n=17). Differences in patient characteristics, including age, gender, stage, treatment protocol, and therapy duration, were not statistically significant. A summary of these details is presented in table 1. Acute adverse events such as mucositis, acute dermatitis, and acute dysphagia were compared between the two groups, revealing no statistically significant differences. However, a higher incidence of high-grade (grade 3) dermatitis was observed in the placebo group (35.3% vs. 11.1%).

Conversely, a higher incidence of high-grade (grade 3) mucositis was noticed in the intervention group (38.9% vs. 11.8%). A summary of the relevant details is presented in table 2. Hematologic acute adverse events were assessed, indicating no significant differences in anemia, leukopenia, or thrombocytopenia when comparing the two groups. Details are provided in table 2. The RR between the two groups was described, with a complete response rate of 83.3% in the intervention group compared to 64.7% in the placebo group. However, this difference did not reach statistical significance ($P = 0.592$).

The median OS was 22 months (confidence interval (CI) 95% = 6.3-37.6) in the statin group and 17 months (CI 95% = 4.9-29.1) in the control group ($P = 0.50$). Likewise, the median PFS was 20 months (CI 95% = 15.8-24.1) in the statin group and 15 months (CI 95% = 8.2-21.7) in the control group ($P = 0.609$). The 5-year OS rates

were 25% (CI 95% = 4-46) in the statin group and 18% (CI 95% = 0-37) in the control group. Correspondingly, the 2-year OS rates were 49% (CI 95% = 26-72) in the statin group and 41% (CI 95% = 18-64) in the control group. The 5-year PFS rates were 17% (CI 95% = 0-34) in the statin group and 18% (CI 95% = 0-37) in the control group. Similarly, the 2-year PFS rates were 33% (CI 95% = 14-52) in the statin group and 24% (CI 95% = 5-43) in the control group. Details of the 2-year and 5-year events are summarized in table 3 and illustrated in figures 1, 2, and 3. Table 4 summarizes the late toxicity score rates concerning dysphagia, laryngeal mucositis, xerostomia, and superficial soft tissue fibrosis during the follow-up period. The median follow-up duration for the statin and control groups was 22 and 17 months, respectively.

Discussion

The study prescribed lovastatin at 80 mg daily, concurrent with definitive CRT in locally advanced HNSCC for the statin group comprising 18 patients. This was compared with a control group consisting of 17 patients. After five years of follow-up, it was observed that RR, median OS, and PFS were non-significantly better in the statin group. The acute and chronic adverse events did not show significant differences.

HNSCCs are among the most common cancers, and CRT is the treatment of choice in unresectable LAHNC.[1, 2] Lipids are one of the basic structures of cell membranes.[5] Recent studies have recognized lipid metabolism as a hallmark of malignancy.[4] Lipids contribute to cell signaling by a group of proteins that are claimed to be upregulated in different cancers that subsequently stimulate tumor growth.[6] Statins inhibit lipid metabolism by preventing HMG-CoA reductase that regulates the activity of signaling proteins called the GTPase superfamily that contributes to tumorigenesis, proliferation, and survival of tumor cells.[7, 3] Several lines of evidence suggest that statins impair the metastatic potential of tumor cells by inhibiting cell migration, attachment to the extracellular matrix, and invasion of the basement membrane. In addition, they have antiangiogenic effects.[13]

Inflammatory risk factors, such as obesity, diabetes mellitus, and smoking, are carcinogenic even without hyperlipidemia; therefore, inflammatory suppression reduces both cardiovascular and cancer mortalities.[14] Statins have anti-inflammatory effects that contribute to

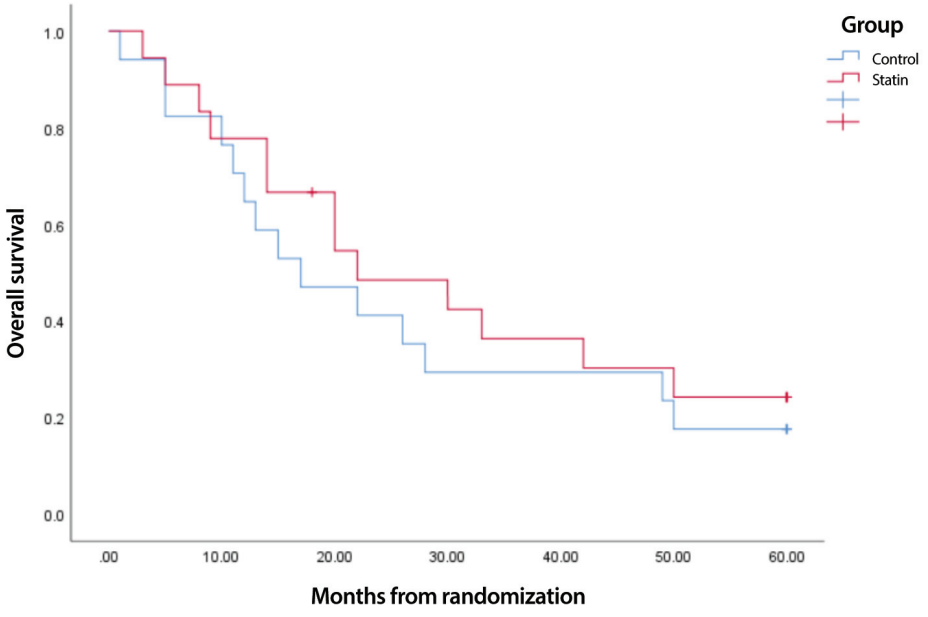

Figure 1. This figure illustrates the OS curve in the control group (blue line) and the statin group (red line). The median OS is 22 months (CI95%=6.3-37.6) in the statin group and 17 months (CI95%=4.9-29.1) in the control group (P = 0.50).
OS: Overall survival; CI: Confidence interval

their beneficial effects independent of lowering cholesterol.[15] In vivo studies have shown that statins have antiproliferative and radiosensitizing effects.[3] They increase sensitization to radiation by stopping the cell cycle in the late G1 phase.[6] Statins are relatively inexpensive and safe with predictable side-effects, with the most common at standard dosing reported as transient gastrointestinal upset and headaches.[8, 12]

Lovastatin apoptotic properties have been demonstrated among several tumors, such as monomyelocytic leukemia, rhabdomyosarcoma, medulloblastoma, astrocytoma, SCC of the head and neck, and cervical SCC.[8, 9] Studies have shown that cholesterol optimization should be considered in all patients with cancer due to a reduction in both cardiovascular and cancer-specific mortalities; therefore, it seems that statins can be prescribed in patients who have clinical indications.[12] A phase I clinical trial showed disease stabilization in HNSCCs with high-dose lovastatin.[8] In the present study, lovastatin was administered at 80 mg/day in divided doses on treatment days.

As most studies were retrospective and primarily performed on common-site malignancies, such as breast, colon, and prostate, the current study, an interventional investigation on head and neck cancers, is unique. Some meta-analyses showed that statins could improve OS and reduce all-cause mortality.[10, 16] Subgroup analysis showed that post-diagnosed statin users gained more benefits,[16, 17] especially in prostate subgroups.[18] However, the results regarding the association of statin therapy and prostate cancer are controversial.[19, 20, 21] Other studies on colorectal cancers showed that both pre-diagnosed and post-diagnosed statin users had significant OS benefits.[14, 22, 23] As a result, the best prescription sequence remains unknown.

In a retrospective study performed on 1,592 HNSCC patients, subjects whose lipid profiles were available a year before treatment and underwent at least one year of follow-up were included. Statin users were defined as those with at least three prescriptions filled a year before diagnosis and at least three filled since diagnosis, if the patient was still alive.[11] Patients with hyperlipidemia who received statins showed improvement in OS and DSS, compared with the other two groups, including those without hyperlipidemia who were under statin therapy

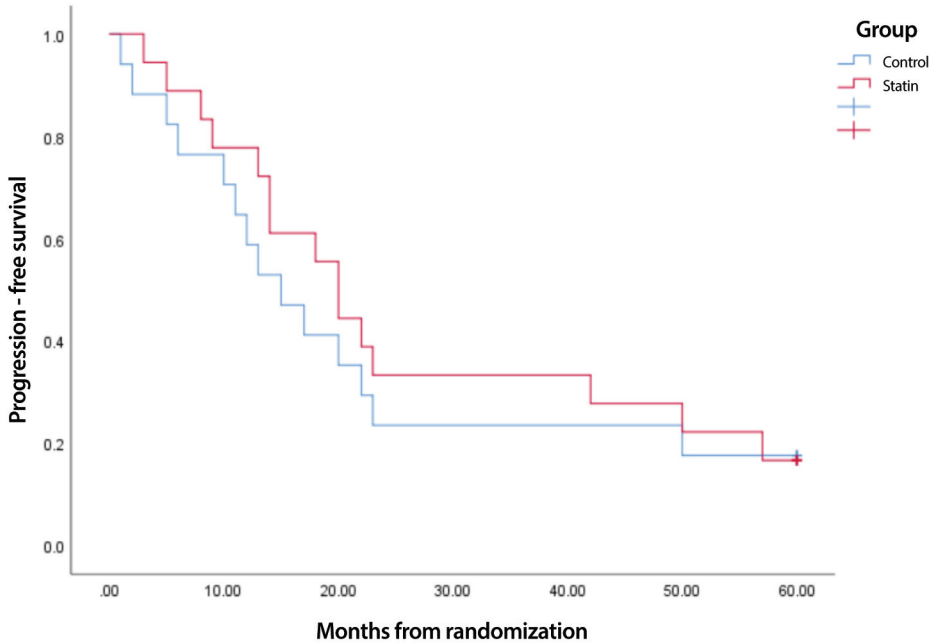

Figure 2. This figure depicts the PFS curve in the control group (blue line) and the statin group (red line). The median PFS is 20 months (CI95%=15.8-24.1) in the statin group and 15 months (CI95%=8.2-21.7) in the control group (P = 0.609).
PFD: Progression-free survival; CI: Confidence interval

Table 4. 2-year and 5-year late reactions: dysphagia, xerostomia, soft tissue fibrosis, laryngeal mucositis. (Grading based on CTCAE v4.0)

Adverse events	Statin group (n=18)	Placebo group (n=17)	
Dysphagia 2 years			
Not measurable	50%	58.8%	1
G1	33.3%	29.4%	
G2	16.6%	11.7%	
Dysphagia 5 years			0.999
Not mentioned	83.3%	88.2%	
G1	5.5%	5.8%	
G2	11.1%	5.8%	
Xerostomia 2 years			
Not mentioned	50%	58.8%	0.998
G1	27.7%	35.2%	
G2	22.2%	5.8%	
Xerostomia 5 years			0.999
Not mentioned	83.3%	88.2%	
G1	5.5%	5.8%	
G2	11.1%	5.8%	
Superficial soft tissue fibrosis 2 years			0.996
Not mentioned	50%	58.8%	
G1	0.0%	0.0%	
G2	50%	41.1%	
Superficial soft tissue fibrosis 5 years			0.999
Not mentioned	83.3%	88.2%	
G1	0.0%	0.0%	
G2	11.1%	5.8%	
G3	5.5%	5.8%	
Laryngeal mucositis 2 years			1
Not mentioned	44.4%	47%	
G1	22.2%	5.8%	
G2	27.7%	23.5%	
G3	5.5%	23.5%	
Laryngeal mucositis 2 years			1
Not mentioned	83.3%	88.2%	
G1	5.5%	5.8%	
G2	5.5%	5.8%	
G3	5.5%	0.0%	

G0: Grade 0; G1: Grade 1; G2: Grade 2; G3: Grade 3; CTCAE: Common Terminology Criteria for Adverse Events

and those who neither had hyperlipidemia nor used statins.[11] In the above-mentioned study, the patients were older than 66, and most underwent surgery and radiotherapy but not chemotherapy.[11] In the current study, there was no evaluation of lipid profile and whether the patients were statin users; however, this study is unique as it is a randomized clinical trial with homogeneous groups regarding the mean age and disease stage.

In another retrospective study conducted on 1,194 HPV-negative HNSCC patients, 572 patients (47.9%) received statins at the time of diagnosis with a minimum of 1 month before diagnosis and at least 4 months after that. Additionally, 622 (52.1%) patients served as controls without statin usage within a minimum of 1 year of their diagnosis date. The results demonstrated statistically significant benefits in the case group, compared with those of the control group, for both median OS and DSS. All participants were older than 65, and comorbidity was higher in the case group. It is interesting to note that the level

of DSS improvement was higher than that of OS; this finding might suggest that the benefit of statins is specifically achieved through targeting the patient's cancer, as opposed to generally improving his/her health status.[12]

The only prospective study for the role of statins in the combination of radiotherapy is the study of Razmjoo et al. that has been performed at Jundishapour University for using lovastatin in patients with advanced head and neck cancer and showed that lovastatin improved non-significant RR in combination with chemoradiation with cisplatin in this group of patients.[24] This study showed that lovastatin could improve objective RR without more acute adverse effects of treatment than the control group. However, the long-term outcomes of patients were not mentioned in the study conducted by Razmjoo et al. Although the study is similar to Razmjoo et al.'s, there are some advantages. This study evaluated the RR 12 weeks after treatment, which is more extended than the 8 weeks used in Razmjoo's study. Additionally, long-term follow-ups were conducted for 2 and 5 years to assess PFS, OS, and late adverse effects. This study confirms the previous research on the role of lovastatin in combination with CRT in head and neck cancer and the positive possibility of the role of statins in cancer treatment. Both studies suffer from the limitation of having an insufficient number of patients included in the study; therefore, to adequately answer the efficacy and proper role of statins in cancer treatment, prospective randomized studies with appropriate design (concurrent or long-term adjuvant use of statins) and a more significant number of patients with longer follow-up are needed. More advanced radiation techniques, such as intensity-modulated radiation therapy, would primarily affect the adverse events and should be used in future trials.

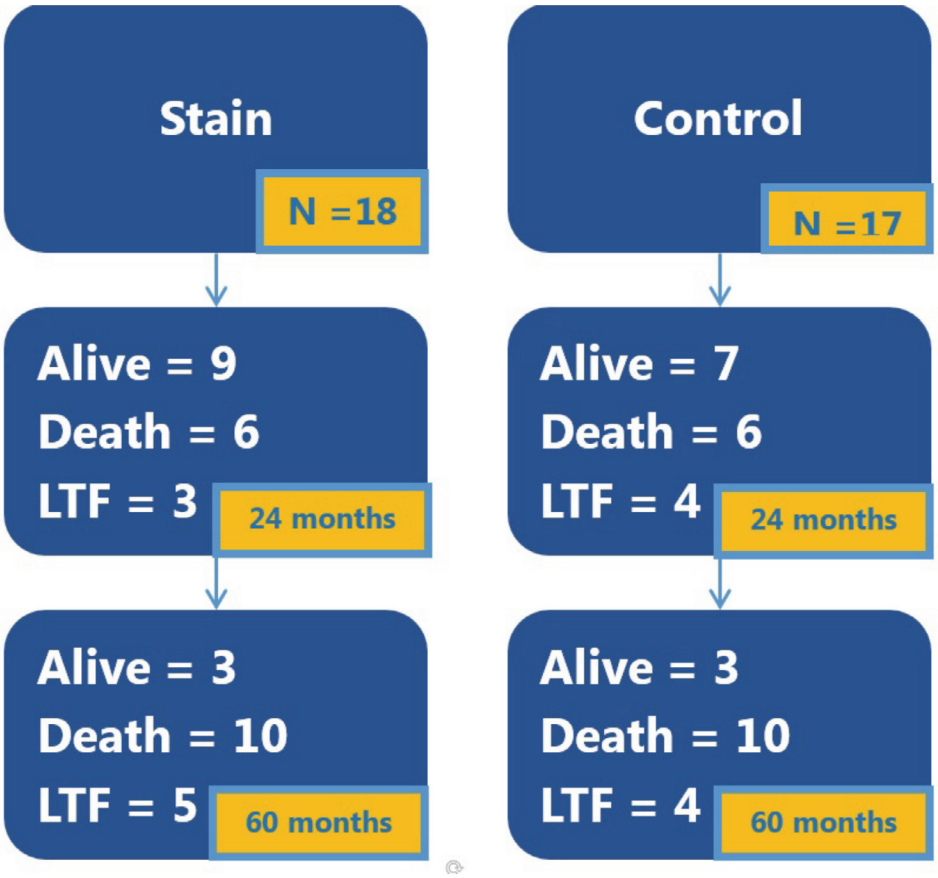

Figure 3. This flow diagram illustrates the statin and control groups' 2- and 5-year follow-ups.
LTF: Lost to follow-up

Conclusion

In the current investigation, statin therapy was administered concurrently with radiotherapy to harness its radiosensitizing properties. Nevertheless, the statin group exhibited marginally improved RR, PFS, and OS, alongside some observed side-effects, albeit without reaching statistical significance. This outcome may be attributed to the limited sample size, prompting us to conclude this study prematurely. However, it is essential to underscore the uniqueness of this study, which incorporated randomization and sustained long-term follow-up. Furthermore, patients may accrue lasting benefits from prolonged statin use.

Additionally, evaluating patients' lipid profiles and their potential implications for patient outcomes is strongly recommended. This study is relatively tiny participant pool can be attributed to the limited number of patients seeking treatment at our facility during the study period and suboptimal patient recruitment. Therefore, advocating for conducting randomized trials with more extensive participant cohorts is essential. Moreover, further research is warranted, encompassing randomized studies with larger patient cohorts undergoing definitive or adjuvant radiotherapy, employing cutting-edge techniques such as intensity-modulated radiotherapy.

Conflict of Interest

None declared.

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