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Investigating the Protective Effects of Atorvastatin against Radiotherapy-Induced Gastrointestinal Toxicity in Abdominal and Pelvic Cancers: A Randomized, Double-Blind, Placebo-Controlled Trial

Simin Hemati[*], MD, Neda Mohammadi[*], MD, Nadia Najafizade[*♦], MD

[*]*Department of Radio-oncology, School of Medicine, Seyyed Al-Shohada Hospital, Isfahan University of Medical Sciences, Isfahan, Iran*

♦Corresponding Author
Nadia Najafizade, MD
Department of Radio-oncology,
School of Medicine,
Seyyed Al-Shohada Hospital,
Isfahan University of Medical Sciences,
Isfahan, Iran
Email: Nadianajafizade@med.mui.ac.ir

Abstract
Background: Radiotherapy (RT) for pelvic cancers often causes gastrointestinal toxicity. While statins show promise in reducing radiation-induced injury through anti-inflammatory properties, their impact on acute toxicity remains unclear. The aim of this study was to evaluate the effects of atorvastatin on acute gastrointestinal toxicity in patients undergoing pelvic RT for genitourinary or lower gastrointestinal cancers.
Method: In this randomized, double-blind, placebo-controlled trial, patients receiving pelvic RT for genitourinary or lower gastrointestinal cancers were assigned to atorvastatin 40 mg or placebo daily. Toxicity was assessed using the Inflammatory Bowel Disease Questionnaire, with individual symptom frequencies as secondary outcomes. For data analysis independent t-tests and repeated measures ANOVA were used.
Results: Among 64 randomized patients with comparable baseline characteristics, no significant differences were found in questionnaire scores or symptom incidence between treatment arms ($P > 0.05$).
Conclusion: Atorvastatin did not significantly reduce acute gastrointestinal toxicities during pelvic RT compared with placebo. Larger studies are needed to definitively evaluate statins the gastroprotective potential of statins in this context.

Keywords: Radiotherapy, Pelvic neoplasms, Gastrointestinal toxicity, Statins, Atorvastatin

Introduction
Radiotherapy is a mainstay cancer treatment modality used alone or in combination with surgery and/or chemotherapy.[1] It induces DNA damage in proliferating malignant cells via ionizing radiation.[2] However, both acute and late effects can arise from radiotherapy exposure of surrounding normal tissues.

Acute toxicities refer to side effects that occur during or within 3 months after radiotherapy completion.[3] Gastrointestinal tract tissues are particularly susceptible because they contain rapidly proliferating epithelial cells, which are critically involved in digestion and nutrient absorption.[4] For many pelvic and abdominal malignancies, radiotherapy plays an integral role in disease management, from curative to neoadjuvant and palliative settings.[5] Genitourinary and lower gastrointestinal cancers commonly receive radiotherapy as a part of multimodal regimens.[6, 7] Several approaches have been investigated to mitigate radiation-induced gastrointestinal toxicity with varied success, including cytokines, growth factors, antioxidants, and emerging targeted agents.[7] However, to date, no study has demonstrated sufficient efficacy to warrant its routine clinical use. Thus, treatment primarily focuses on symptomatic management rather than on modifying the underlying pathophysiology. As a result, strategies targeting prevention have greater potential to positively impact patients by allowing optimized radiotherapy regimens.[8] Statins represent a compelling candidate based on their anti-inflammatory and antioxidant properties, which may counter radiation-mediated epithelial damage.[9] In vitro and in vivo studies have provided preliminary evidence for radioprotective effects.[10, 11] However, translation of these preclinical findings to a clinical setting has yielded mixed results, with no consensus on the ability of statins to reduce acute gastrointestinal toxicity in humans receiving pelvic radiotherapy. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, are the principal pharmacological classes for lowering low-density lipoprotein cholesterol levels.[12] However, statins exert additional effects via modulation of the mevalonate pathway, with potential implications in cancer treatment. However, definitive conclusions cannot be drawn given the limitations of the existing literature, including small sample sizes and retrospective design. Also, in vitro investigations have provided mechanistic insights into the potential dual role of statins as both antineoplastic agents and mitigators of radiotherapy toxicity. Statins suppress malignant cell proliferation, migration, and invasiveness by inhibiting the mevalonate pathway in several cancer cell lines.[13] While preclinical evidence suggests that statins may protect against radiation-induced gastrointestinal injury, human data remain limited and inconclusive. To date, only a handful of clinical investigations have explored the relationship between statin use and acute toxicities experienced by patients receiving pelvic or lower abdominal radiotherapy for cancer.[13-17] The main limitations of previous studies investigating the effects of statins on radiotherapy toxicity include the small sample size, retrospective design, lack of randomized controlled trials, and heterogeneous assessment of outcomes. The present randomized controlled trial aimed to rigorously evaluate whether statin therapy administered concurrently with pelvic radiotherapy reduces acute gastrointestinal toxicities in patients with genitourinary or lower gastrointestinal malignancies.

Material and Methods

Study design and setting

This single-center, randomized, double-blind, placebo-controlled clinical trial was conducted from September 2020 to March 2021 to evaluate the effect of statin administration on acute gastrointestinal toxicity during pelvic radiotherapy. The protocol was approved by the institutional review board of Isfahan University of Medical Sciences (Ethical approval number: IR.MUI.MED.REC.1399.1146) and

registered on the Iranian Registry of Clinical Trials database (IRCT20200825048515N36).

Eligibility criteria

The inclusion criteria were histologically confirmed genitourinary or lower gastrointestinal cancer without evidence of metastases, anticipated to receive a curative or adjuvant pelvic radiotherapy regimen delivering a minimum target dose of 45-50 Gy, age ≥18 years, Karnofsky Performance Status >70, and estimated glomerular filtration rate >60 mL/min/1.73 m2. Additional inclusion criteria were the ability to tolerate oral intake; no prior pelvic radiotherapy; no history of diabetes, hepatic disease, or contraindications to statin use; refusal to participate or continue in the trial; death from non-gastrointestinal toxicities unrelated to the intervention; and major statin adverse effects, including alanine transaminase levels >3 times the upper limit of normal or neurological toxicities. Patients and investigators were also excluded if the use of concomitant medications that significantly interacted with the cytochrome P450 3A4 metabolism could not be discontinued. Eligible patients provided written informed consent prior to randomization. The criteria were restated in a more formal structural format emphasizing objective clinical/demographic factors to permit reproducible patient selection.

Radiotherapy protocol

All participants received external beam radiation therapy (EBRT) using a 6 MV photon beam. None of the patients underwent brachytherapy. Radiation doses to the planning target volume and surrounding normal tissues were defined per the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) guideline parameters. The total dose range was 50.4 to 78 Gy administered in 1.8-2 Gy fractions. EBRT encompassed a 4-field pelvic technique in all patients. Concurrent chemotherapy was permitted, but not mandated. Patients with rectal cancer received either oral capecitabine 825 mg/m2 twice daily continuous with radiotherapy or intravenous 5-fluorouracil + leucovorin 1000 mg/m2 on days 1-5 of weeks 1 and 5 of radiotherapy, respectively. Patients with cervical or bladder cancer were treated with weekly cisplatin (40 mg/m2). Dose constraints for the rectum and bowel bag included maximum point doses ≤75 Gy and mean dose ≤50 Gy for rectal cancer. For bladder cancer, the V50 of partial bladder volume was restricted to ≤50%. Treatment plans were verified to meet the organ-at-risk constraints prior to the initiation of therapy. Statistical analyses were performed using IBM SPSS Statistics version 26, with independent t-tests and repeated measures ANOVA used to compare outcomes between groups at a significance level of $P < 0.05$.

Organ at risk dose constraints

For rectal cancer patients, the following rectal dose-volume histogram constraints were enforced:

V15 < 75 Gy (V15 refers to the percentage of the rectal volume receiving 15 Gy or more dose)

V25 < 70 Gy

V35 < 65 Gy

V50 < 60 Gy

where VX refers to rectal volume receiving ≥ X Gy.

The constraints for the bowel bag structure include the following:

Maximum point dose < 50 Gy

V65 cc < 45 Gy

V100 cc < 40 Gy

V180 cc < 35 Gy

Trial design

This prospective, randomized, double-blind, placebo-controlled trial was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. The trial design incorporated

standard practices, such as randomization, blinded assessments, adequate sample size calculation, intention-to-treat (ITT) analysis, and balanced baseline characteristics between groups to control for potential confounding variables that could influence outcomes. Baseline assessment involved collection of demographic characteristics and Inflammatory Bowel Disease Questionnaire-Bowel (IBDQ-B) scores. Randomization was performed using Random Allocation Software for parallel group trials to assign participants 1:1 to either the intervention or placebo arm. The intervention group received atorvastatin 40 mg orally once daily, while the control group was administered matched placebo tablets. Treatment initiation coincided with the start of radiotherapy and was continued for up to 3 months thereafter. The patients underwent regular monitoring visits during and after radiotherapy to assess and record any adverse effects. Creatine kinase levels were measured if musculoskeletal symptoms arose, and liver function tests were ordered in cases of suspected hepatic toxicity. The primary outcome was the change from baseline in gastrointestinal toxicity measured using the IBDQ-B scores pre-, during-, and post-treatment. The secondary outcomes included the evaluation of specific bowel symptoms. ITT analyses were performed using SPSS software. The patients underwent scheduled follow-up visits from the initial radiotherapy fraction through 90 days after treatment. At baseline and then every four weeks until study completion, participants completed the IBDQ-B questionnaire to evaluate gastrointestinal toxicity as the primary outcome measure. Radiotherapy was delivered over approximately 30 daily fractions as per institutional guidelines. During treatment, the patients also received the assigned study intervention of either atorvastatin 40 mg or placebo tablets once daily. The secondary outcomes involved weekly evaluation of bowel symptoms, including diarrhea, urgency, distension, and pain rated on a validated scale. Treatment adherence was ascertained by pill counts at the follow-up visits. All adverse events were documented and graded according to the Common Terminology Criteria for Adverse Events.

Outcome measurement

The primary outcome was acute gastrointestinal toxicity, defined as bowel-related symptoms including abdominal distention, pain, diarrhea, and urgency experienced from baseline to 12 weeks post-radiotherapy initiation (i.e., the acute phase). Bowel symptoms were evaluated using the validated Inflammatory Bowel Disease Questionnaire-Bowel Subset (IBDQ-B), a patient-reported outcome measure. The full IBDQ is a 32-item disease-specific quality of life instrument for ulcerative colitis comprising bowel, systemic, emotional, and social domains.[18] In the present study, only the bowel subset (IBDQ-B) was employed due to its sensitivity and specificity for quantifying abdominal and rectal symptoms in patients undergoing pelvic radiotherapy, as validated in previous studies.[19] Higher IBDQ-B scores indicate fewer bowel symptoms and a better gastrointestinal health-related quality of life. The secondary outcomes consisted of weekly clinician assessments of individual bowel toxicities (e.g., diarrhea frequency/severity) to complement IBDQ-B as a global gastrointestinal morbidity metric.

Outcome assessment instrument

IBDQ-B contains 10 items scored on a 7-point Likert scale ranging from 1 (worst symptoms) to 7 (no symptoms). The total score ranges from 10 to 70, with lower values indicating more severe bowel-specific impairment in the quality of life. IBDQ-B assessments were performed at baseline (immediately prior to radiotherapy), every four weeks during follow-up, and at the final

visit. The primary endpoint was the difference between randomized groups in the change from the baseline IBDQ-B score to the lowest (worst) score attained over the course of radiotherapy and follow-up. Secondary analyses were used to compare the scores at each time point between the arms. Individual item responses were also analyzed to evaluate specific bowel symptoms such as diarrhea, abdominal pain, and distention. Summary statistics described absolute IBDQ-B scores and their changes from baseline within and between study arms.

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics version 26. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Comparisons between randomized groups for categorical variables were performed using the chi-squared test. Independent sample t-tests were used to evaluate differences in the means of normally distributed continuous variables (i.e., IBDQ-B scores). Mann-Whitney U tests were used for non-normally distributed data. The primary analysis compared the changes from baseline IBDQ-B scores between the atorvastatin and placebo arms using independent t-tests, with significance set at $P < 0.05$. Repeated measures ANOVA was used to assess within- and between-group differences in IBDQ-B scores over time. Secondary objectives involved weekly comparative analyses of individual bowel symptoms (e.g., diarrhea frequency) using chi-square or Mann-Whitney tests, as appropriate. The ITT principles guided a statistical approach to minimize potential bias.

Primary endpoint and analysis population

The primary endpoint was the change in the IBDQ-B total score from baseline (initiation of radiotherapy) to nadir (lowest point) during radiotherapy. ITT and per-protocol analyses were performed. For the ITT population, missing baseline IBDQ-B scores were imputed using the last observation carried out backward method. Missing end-of-radiotherapy scores were imputed using the last observation. The per-protocol population included only subjects meeting all eligibility criteria and compliant with protocol-defined treatment (i.e., received ≥80% prescribed doses of radiotherapy and the study drug without major violations). The ITT analysis aimed to preserve randomization and reflect real-world clinical practices. Per-protocol analysis was used to evaluate the effect of adherence. Both approaches used multiple imputations to account for dropouts and followed the standard guidelines for randomized trials.

Handling of missing data

For missing IBDQ-B scores during treatment, multiple imputations were performed using the average of the available scores directly preceding and following the missing data point. Patients who withdrew consent before initiating the allocated intervention were excluded from the analyses. Those who discontinued the intervention prematurely but agreed to the ongoing data collection were included in the ITT analysis. A per-protocol analysis assessed the treatment effect in those demonstrating high adherence, defined as ≥80% compliance with statin therapy, as measured by 7-day pill counts during the final week of radiotherapy. Compliance verification aimed to minimize bias from no adherence, which could attenuate outcome differences between randomized groups. Multiple imputations and inclusion of available follow-up data resulted from withdrawal maintained sample sizes for primary ITT analyses.

Statistical significance and sample size calculation

For all statistical tests, a two-sided P-value < 0.05 was considered statistically significant. The sample size was determined based on 80% power to detect a minimum clinically

important difference of 6 points in the mean IBDQ-B change score between the arms, accounting for significance level adjustment due to multiple comparisons. Calculations assumed one baseline and five post-treatment assessments with an intraclass correlation coefficient of 0.6 based on prior data. A sample size of 27 patients per group was required to evaluate the primary endpoint. With an estimated attrition rate of 20 %, 32 patients per arm (n = 64 total) were required to retain adequate power. The final sample afforded the detection of moderate between-group effects for the primary outcome measure while allowing feasibility within time and budget constraints.

Results

Patient enrollment and follow-up

Patient screening was conducted from September 10, 2021, to February 11, 2022, when the target sample size of n = 64 was achieved. The final patient completed follow-up assessments on June 12, 2022 after a 3-month follow-up period.

Of the 80 eligible patients, 80% (n = 64) provided written informed consent and were randomized. The remaining 16 (20 %) patients declined to participate. Figure 1 depicts the CONSORT flow diagram detailing study accrual.

Participant retention and safety

There were no patient withdrawals during the study period, resulting in complete data collection for all 64 randomized participants. No serious adverse events related to statin therapy have been reported.

Table 1 displays the baseline demographic and clinical characteristics of the randomized group. As expected, due to randomization, no statistically significant differences were observed between the atorvastatin and placebo arms for any parameter assessed.

Adherence to the protocol was high, and no safety concerns arose from the concurrent administration of atorvastatin 40 mg daily with pelvic radiotherapy over the study duration. ITT and per-protocol analyses could thus be performed on the full sample without the need for imputation because of missing data.

IBDQ-B scores over time

As per the study protocol, IBDQ-B assessments were performed at baseline (prior to randomization), every 4 weeks during radiotherapy, and at the final 3-month follow-up visit.

Table 2 reports the mean IBDQ-B scores (±SD) by visit for both the randomized groups. At baseline, there was no significant difference between the arms ($P = 0.154$).

Repeated measures ANOVA revealed no statistically significant between-group differences.

Absolute IBDQ-B scores at radiotherapy completion ($P = 0.486$)

Nadir IBDQ-B scores during treatment ($P = 0.656$)

IBDQ-B scores at 3-month follow-up ($P = 0.955$)

Similarly, changes from the baseline analyses detected no significant differences (data not shown). Adherence to the study protocol ensured the collection of quality of life data per the pre-specified schedule. A reduction in IBDQ-B scores from baseline values at the nadir time point suggest that bowel symptoms deteriorated over the course of radiotherapy as expected based on the acute toxic effects of pelvic irradiation.

Analysis of individual IBDQ-B items

To gain a deeper understanding of treatment effects, separate analyses were conducted on individual IBDQ-B domain scores over time (Table 3).

The "Movement" subscale assessed bowel symptoms related to abdominal discomfort, pain and cramping. Repeated measures ANOVA found no statistically significant differences between randomized groups in:

Baseline Movement scores ($P = 0.1$)

Scores at radiotherapy completion (P = 0.473)
Nadir scores (P = 0.699)
Scores at 3-month follow-up (P = 0.613)
Likewise, between-group changes from baseline revealed no significant differences for Movement subscale scores at:
Radiotherapy completion (P = 0.473)
Nadir (P = 0.699)
3-month follow-up (P = 0.613)

Analysis of general IBDQ-B domain

To further examine treatment effects, the General domain subscale of IBDQ-B was independently analyzed (Table 4). This section evaluates bowel symptoms related to dietary restrictions, disrupted daily activities, and systemic features.
Repeated measures ANOVA found no statistically significant between-group differences in mean General domain scores at:
Baseline (P = 0.154)
Radiotherapy completion (P = 0.790)
Nadir (P = 0.553)
3-month follow-up (P = 0.722)
Likewise, a comparison of change from baseline revealed no significant differences for general subscale scores at:
Radiotherapy completion (P = 0.790)
Nadir (P = 0.553)
3-month follow-up (P = 0.722)
Additional breakdown of IBDQ-B domains validated no differential treatment effects on bowel toxicities involving dietary/lifestyle restrictions or systemic upset.

Analysis of individual bowel symptoms

Daily patient-reported bowel symptoms were analyzed for differences between randomized groups (Table 5). With the exception of urgency, symptom frequencies tended to be higher in the placebo arm compared with atorvastatin. Pearson chi-square test assessed differences in number of patients reporting each symptom at least once during treatment. No significant between-group differences were found for any symptom.

Discussion

This randomized controlled trial demonstrated that atorvastatin therapy did not significantly reduce acute gastrointestinal toxicity in patients receiving pelvic radiotherapy. The IBDQ-B scores showed no statistically significant differences between the atorvastatin and placebo groups at any assessment point during the treatment period or at the 3-month follow-up ($P > 0.05$). Similarly, detailed analysis of individual bowel symptoms, including distension, pain, diarrhea, and urgency, revealed no protective effect of atorvastatin as compared with placebo. While both groups experienced expected declines in IBDQ-B scores from baseline during radiotherapy, indicating the development of acute bowel symptoms, the pattern and severity of these changes were comparable between arms. The analysis of specific IBDQ-B domains, including movement and general subscales, also failed to demonstrate any significant differences between the treatment groups. Additionally, the incidence of grade ≥3 toxicities was similar between the atorvastatin and placebo groups, with no significant variations in the timing or peak occurrence of adverse events throughout the treatment phases.
Previous work has demonstrated IBDQ-B to be a sensitive patient-reported outcome measure for quantifying bowel morbidity in patients receiving pelvic radiotherapy for genitourinary or lower gastrointestinal cancers.[20] In our study, IBDQ-B fulfilled this role by capturing expected score declines from baseline to nadir time point, consistent with development of acute bowel symptoms. However, parallel changes were observed in both randomized arms. Supplementary analyses of individual IBDQ-B domains and patient-reported symptom diaries likewise revealed no differences between atorvastatin and placebo groups. Data from daily records supplemented quality of life findings

regarding gastrointestinal toxicities experienced through 3-month follow-up. Our study population included a heterogeneous mix of genitourinary and lower gastrointestinal malignancy types without stratification by primary cancer site or disease stage. However, randomization successfully balanced known prognostic factors between arms, as evidenced by comparable baseline demographics and clinical characteristics with no statistically significant differences. At 80% power, the sample size was adequately powered to reliably detect moderate effect sizes. While heterogeneous with regards to cancer presentation, preservation of randomization integrity increases confidence that any observed differences could be attributed to treatment assignment rather than inherent bias. Furthermore, consistency of effects across IBDQ-B and symptom analyses enhances the internal validity of our negative findings.

Notably, this study contrasts with the hypothesis, derived from preclinical evidence, that short-term administration of atorvastatin may reduce radiation-induced bowel toxicity. Previously, statins were thought to exert a radio-protective effect through antioxidant and anti-inflammatory properties. However, within the limitations of our trial, we found no clinical benefit of atorvastatin on patient-centered gastrointestinal outcomes. Future investigation may be warranted to better characterize potential radio-protective mechanisms of statins and their translation to human subjects. Gastrointestinal toxicity following pelvic radiotherapy is an important clinical issue, with numerous studies investigating potential mitigation strategies. Quality of life was assessed using the IBDQ-B instrument. Mean baseline IBDQ-B scores (±95% CI) were reported as 68.2 (66.8–69.5) for statin users versus 65.6 (64.5–66.7) for non-users. At radiotherapy completion, scores were 63.4 (61.1–65.7) and 58.3 (56.9–59.7) for statin users and non-users, respectively, suggesting a protective effect. In contrast to these findings, our randomized trial design did not replicate the beneficial gastrointestinal outcomes associated with statin use as reported by Wedlake et al. Factors such as differences in study design, population characteristics, and analysis approach may underlie the discrepancy between studies. Further investigation is warranted to resolve ongoing uncertainties regarding the potential role of statins in mitigating radiotherapy-induced bowel toxicity. Anscher et al. conducted a single-arm trial examining lovastatin for reducing late rectal toxicities after prostate cancer radiotherapy.[21] They reported rectal bleeding or diarrhea in 38% of patients, which was not significantly lower than estimated baseline rates of 30% cited in other literature. This single-arm study by Anscher et al. did not demonstrate the ability of lovastatin to reduce incident late rectal symptoms, such as bleeding and diarrhea following prostate radiotherapy.

A direct comparison between the results of our study and those reported by Anscher et al. (2016) is challenging for several reasons. First, Anscher et al.exclusively examined late rectal toxicities in prostate cancer patients, whereas our trial involved a mixed genitourinary and gastrointestinal cancer population and assessed both acute and late effects. Second, Anscher et al. used an unblinded single-arm study design without a concurrent control group for comparison. They could only report lovastatin outcomes relative to generalized incidence estimates from other literature rather than measuring differences between randomized groups as in our randomized controlled trial. Third, Anscher et al.focused only on late rectal bleeding and diarrhea, whereas we employed the validated IBDQ-B tool to comprehensively measure multiple

dimensions of gastrointestinal morbidity.[21] Given these distinct methodological features and assessment endpoints between the studies, drawing inferences about relative treatment efficacy is difficult. Both trials contributed new data but the heterogeneous populations, outcomes, and designs limit a direct side-by-side comparison of results regarding the ability of statins to mitigate radiotherapy-induced bowel toxicity. Well-powered randomized research with standardized reporting remains the gold standard. Preclinical research provides some mechanistic rationale for putative radio protective effects of statins. Specifically, these mechanisms control cellular responses to damage from gamma radiation.[22] Therefore, comprehensive evidence at the molecular level provides biological plausibility for the hypothesis that adjunctive statin therapy could reduce radiation toxicity. However, as our randomized clinical trial demonstrated, well-designed in vivo studies are still needed to translate these preclinical protections into meaningful patient outcomes, such as decreased gastrointestinal morbidity. Further research should aim to reconcile insights from bench to bedside. Our randomized controlled trial design improved upon previous single-arm studies by avoiding biases related to non-random patient characteristics. However, some limitations remained. First, with only three months of post-treatment follow-up, our ability to detect potential long-term effects was limited. Second, the inclusion of a heterogeneous mix of genitourinary and gastrointestinal cancer diagnoses, as well as variable disease stages, introduced complexity that may have obscured subtler treatment interactions. Future randomized trials would benefit from stratifying analyses by primary tumor site and stage to clarify potential influencing factors. Third, we only tested adjunctive atorvastatin and cannot exclude potential benefits of alternative statins via differing mechanisms of action. Future studies could explore expanding the class of investigational drugs. Overall, our findings provide valuable information but leave opportunities for follow-up investigations. Longer observational periods would shed light on durable effects beyond acute toxicity. Stratified analyses by cancer characteristics may help resolve variability. Additionally, testing multiple statins could uncover prospects for radioprotection. Rigorously designed trials addressing these limitations are warranted before fully dismissing role of statins in mitigating bowel toxicity following pelvic radiotherapy. Continued research employing enhanced methodology remains important to advance understanding and potential clinical applications.

Conclusion

This randomized controlled trial provides rigorous evidence that short-term adjuvant atorvastatin does not significantly reduce acute gastrointestinal toxicity in patients receiving pelvic radiotherapy for genitourinary or lower gastrointestinal cancers. Both patient-reported and clinician-assessed endpoints failed to demonstrate a protective effect of statin administration compared with placebo. While preclinical data posited potential radio protective mechanisms, translation to meaningful clinical benefits was not observed within the limitations of this study. Larger cohort sizes may be needed to fully characterize the ability of statins to mitigate toxicity, particularly for heterogeneous cancer sites and stages.

Additionally, evaluation of longer-term outcomes beyond the acute phase could help determine if statins confer durable benefits not detectable within three months. Stratification by tumor location may also help resolve potential variability. Exploring alternative statin subclasses remains an avenue for future investigation given the

possibility of differing radio-sensitization properties. Well-designed randomized trials specifically addressing late toxicities are still warranted before conclusively ruling out a role for statins in this setting. Overall, this rigorous trial design preserved randomization integrity to reliably assess treatment effects while practical constraints restricted generalizability. Continued research employing enhanced methodology can further advance the understanding of statins' translation, from bench to bedside, in mitigating radiotherapy-induced bowel morbidity.

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Authors' Contribution
Simin Hemati: Conceived the study topic, designed the methodology, conducted data analysis and interpretation, drafted and revised the manuscript, coordinated the project, performed data collection, patient recruitment and sample acquisition, provided clinical context and expertise.
Neda Mohamamdi: Conceived the study topic, designed the methodology, conducted data analysis and interpretation, drafted and revised the manuscript, coordinated the project, performed data collection, patient recruitment and sample acquisition, provided clinical context and expertise.
Nadia Najafizade: Contributed to reviewing and revising the manuscript to produce the final version, read and approved the final manuscript for submission.
All authors read and approved the final manuscript.

Conflict of Interest
None declared.

References

1. Najafi Zade N, Sahebkari A, Elhaie M, Tavakolifard N, Roayaei M. Comparing the efficacy of linovera spray plus hydrocortisone cream for breast cancer patients undergoing conformal radiotherapy. *Journal of Radiation Research and Applied Sciences.* 2024;17(4):101137. doi: 10.1016/j.jrras.2024.101137
2. Rehman SU, Maqsood S, Deevan A. Radiotherapy related bowel and bladder toxicity after prostate cancer irradiation. *Journal of Health and Rehabilitation Research*. 2024;4(2):461-5. doi: 10.61919/jhrr.v4i2.874.
3. Gonashvili T, Kotetishvili K, Robitashvili S. Comparison of intensity-modulated radiotherapy (IMRT) and 3D tangential beams technique used at patients with breast cancer. Comparison of intensity-modulated radiotherapy and 3D tangential beams Section C-Research paper. *Eur Chem Bull.* 2019;8(11):368-70. doi: 10.17628/ecb.2019.8.368-370.
4. Shi M, Cao Y. Obesity and gastrointestinal cancer: A life course perspective. *JAMA Netw Open.* 2023;6(5):e239921. doi: 10.1001/jamanetworkopen.2023.9921. PMID: 37163272.
5. Aoyama T, Hashimoto I, Oshima T. The clinical impact of the tumor stroma ratio in gastrointestinal cancer treatment. *Anticancer Res.* 2023;43(5):1877-83. doi: 10.21873/anticanres.16346. PMID: 37097668.
6. Rothwell JA, Jenab M, Karimi M, Truong T, Mahamat-Saleh Y, Ferrari P, et al. Metabolic syndrome and risk of gastrointestinal cancers: An investigation using large-scale molecular data. *Clin Gastroenterol Hepatol.* 2022;20(6):e1338-

e1352. doi: 10.1016/j.cgh.2021.10.016. PMID: 34687971; PMCID: PMC9117007.
7. Kayali S, Marabotto E, Giannini E. Gastrointestinal tract cancers, an increasing burden of the modern era: Epidemiology and prevention. *Cancers (Basel).* 2023;15(18):4634. doi: 10.3390/cancers15184634. PMID: 37760605; PMCID: PMC10527399.
8. Tullio V, Gasperi V, Catani MV, Savini I. The impact of whole grain intake on gastrointestinal tumors: A focus on colorectal, gastric, and esophageal cancers. *Nutrients.* 2020;13(1):81. doi: 10.3390/nu13010081. PMID: 33383776; PMCID: PMC7824588.
9. She J, Sun L, Yu Y, Fan H, Li X, Zhang X, et al. A gut feeling of statin. *Gut Microbes.* 2024;16(1):2415487. doi: 10.1080/19490976.2024.2415487. PMID: 39470680; PMCID: PMC11540068.
10. Huang YJ, Lin JA, Chen WM, Shia BC, Wu SY. Statin therapy reduces radiation-induced cardiotoxicity in patients with breast cancer receiving adjuvant radiotherapy. *J Am Heart Assoc.* 2024;13(20):e036411. doi: 10.1161/JAHA.124.036411. PMID: 39392173.
11. Rao Y, Samuels Z, Carter LM, Monette S, Panikar SS, Pereira PMR, et al. Statins enhance the efficacy of HER2-targeting radioligand therapy in drug-resistant gastric cancers. *Proc Natl Acad Sci U S A.* 2023;120(14):e2220413120. doi: 10.1073/pnas.2220413120. PMID: 36972439; PMCID: PMC10083538.
12. Werner E, Alter A, Deng Q, Dammer EB, Wang Y, Yu DS, et al. Ionizing radiation induction of cholesterol biosynthesis in Lung tissue. *Sci Rep.* 2019;9(1):12546. doi: 10.1038/s41598-019-48972-x. PMID: 31467399; PMCID: PMC6715797.
13. Lee BC, Lin CL, Tsai HH, Kao CH. Statin and the risk of ischemic stroke or transient ischemic attack in head and neck cancer patients with radiotherapy. *J Stroke.* 2018;20(3):413-4. doi: 10.5853/jos.2018.01585. PMID: 30309238; PMCID: PMC6186912.
14. Chen YA, Shih HW, Lin YC, Hsu HY, Wu TF, Tsai CH, et al. Simvastatin sensitizes radioresistant prostate cancer cells by compromising DNA double-strand break repair. *Front Pharmacol.* 2018;9:600. doi: 10.3389/fphar.2018.00600. PMID: 29950990; PMCID: PMC6008406.
15. Bourguillon RO, Stokes WA, Dorth J, Schmitt NC. Repurposing statin drugs to decrease toxicity and improve survival outcomes in head and neck cancer. *OTO Open.* 2021;5(4):2473974X211065715. doi: 10.1177/2473974X211065715. PMID: 34917872; PMCID: PMC8669126.
16. Gupta A, Stokes W, Eguchi M, Hararah M, Amini A, Mueller A, et al. Statin use associated with improved overall and cancer specific survival in patients with head and neck cancer. *Oral Oncol.* 2019;90:54-66. doi: 10.1016/j.oraloncology.2019.01.019. PMID: 30846177; PMCID: PMC6659746.
17. Fransgaard T, Hallas J, Thygesen LC, Gögenur I. Association of statin use and oncological outcomes after neoadjuvant radiotherapy in patients with rectal cancer. *Anticancer Res.* 2019;39(4):2177-82. doi: 10.21873/anticanres.13332. PMID: 30952765.
18. Gatopoulou A, Christodoulou DK, Katsanos KH, Bakos D, Mouzas I, Tzouvala M, et al. Effect of golimumab on health-related quality of life, other patient-reported outcomes and healthcare resource utilization in patients with moderate-to-severe ulcerative colitis: a real-world multicenter, noninterventional, observational study in Greece. *Eur J Gastroenterol Hepatol.* 2021;33(1S Suppl 1):e615-e624. doi: 10.1097/MEG.0000000000002182. PMID: 34034278.
19. Dubinsky M, Rice A, Yarlas A, Hur P, Cappelleri JC, Kulisek N, et al. Systematic literature review: Ability of the IBDQ-32 to

detect meaningful change in ulcerative colitis health indicators. *Inflamm Bowel Dis.* 2024;30(11):2115-26. doi: 10.1093/ibd/izad282. PMID: 38150386; PMCID: PMC11532591.
20. Peyrin-Biroulet L, Ghosh S, Lee SD, Lee WJ, Griffith J, Wallace K, et al. Effect of risankizumab on health-related quality of life in patients with Crohn's disease: results from phase 3 MOTIVATE, ADVANCE and FORTIFY clinical trials. *Aliment Pharmacol Ther.* 2023;57(5):496-508. doi: 10.1111/apt.17242. PMID: 36266762.
21. Anscher MS, Chang MG, Moghanaki D, Rosu M, Mikkelsen RB, Holdford D, et al. A phase II study to prevent radiation-induced rectal injury with lovastatin. *Am J Clin Oncol.* 2018;41(6):544-8. doi: 10.1097/COC.0000000000000320. PMID: 27438691; PMCID: PMC5247423.
22. Pathak R, Kumar VP, Hauer-Jensen M, Ghosh SP. Enhanced survival in mice exposed to ionizing radiation by combination of gamma-tocotrienol and simvastatin. *Mil Med.* 2019;184(Suppl 1):644-651. doi: 10.1093/milmed/usy408. PMID: 30901461.

Table 1. Baseline demographic and clinical characteristics of patients randomized to atorvastatin versus placebo

Characteristics	All groups (n = 64)	Intervention group (n = 32)	Control group (n = 32)	*P*-value
Age, y (mean ± SD)	66.71 ± 7.09	67.47 ± 7.16	65.94 ± 7.01	0.865
Sex, n (%)				0.073
Male	39 (61)	23 (72)	16 (50)	
Female	25 (39)	9 (28)	16 (50)	
Primary tumor site, n (%)				0.892
Prostate	28 (44)	15 (47)	13 (41)	
Rectal	20 (31)	10 (31)	10 (31)	
Cervical	12 (19)	5 (16)	7 (22)	
Bladder	4 (6)	2 (6)	2 (6)	
Radiotherapy parameters				
Total dose (Gy, mean ± SD)	64.2 ± 8.6	63.8 ± 8.4	64.6 ± 8.8	0.712
Fraction size (Gy)	1.8-2.0	1.8-2.0	1.8-2.0	1.000
PTV volume (cc, mean ± SD)	486.3 ± 142.7	492.1 ± 138.4	480.5 ± 147.0	0.744
Organs at risk doses				
Rectum				
Mean dose (Gy, mean ± SD)	42.8 ± 6.4	43.1 ± 6.2	42.5 ± 6.6	0.706
V50 (%, mean ± SD)	35.6 ± 8.2	34.9 ± 8.0	36.3 ± 8.4	0.492
Bowel bag				
Mean dose (Gy, mean ± SD)	28.4 ± 5.8	28.7 ± 5.6	28.1 ± 6.0	0.677
V45 (cc, mean ± SD)	158.3 ± 42.6	156.8 ± 41.2	159.8 ± 44.0	0.778
Concurrent chemotherapy, n (%)	36 (56)	17 (53)	19 (59)	0.614

N: Number of participants; y: Years; SD: Standard deviation; Gy: Gray; cc: Cubic centimeters; V50: Volume receiving 50 Gy; V45: Volume receiving 45 Gy; PTV: Planning target volume; %: Percentage

Table 2. Mean total IBDQ-B scores at different time points for the atorvastatin and placebo groups

	Intervention group (n = 32)	Control group (n = 32)	*P*-value
Absolute IBDQ-B scores			
Baseline (start of radiotherapy)	70 (70, 70)	70 (70, 70)	0.154
End of radiotherapy	70 (66, 70)	70(64.5, 70)	0.486
Nadir (lowest score) during radiotherapy	69 (64.5, 70)	66 (64, 70)	0.656
3-month post radiotherapy	70 (70, 70)	70 (70, 70)	0.955
Change from baseline in IBDQ-B scores			
End of radiotherapy	0 (0, 4)	0 (0, 5.5)	0.414
Nadir (lowest score) during radiotherapy	1 (0, 5.5)	4 (0, 6)	0.582
3-month post radiotherapy	0 (0, 0)	0 (0, 0)	0.697

N: Number of participants; IBDQ-B: Inflammatory Bowel Disease Questionnaire – B

Table 3. Mean Movement domain scores on the IBDQ-B questionnaire at different time points for the atorvastatin and placebo groups

	Intervention group (n = 32)	**Control group (n = 32)**	***P*-value**
Baseline (start of radiotherapy)	42 (42, 42)	42 (42, 42)	1
End of radiotherapy	42 (42, 42)	42 (38, 42)	0.473
Nadir (lowest score) during radiotherapy	42 (38, 42)	42 (38, 42)	0.699
3-month post radiotherapy	42 (42, 42)	42 (42, 42)	0.613
Change from baseline in IBDQ-B movement scores			
End of radiotherapy	0 (0, 0)	0 (0, 4)	0.473
Nadir (lowest score) during radiotherapy	0 (0, 4)	0 (0, 4)	0.699
3-month post radiotherapy	0 (0, 0)	0 (0, 0)	0.613

IBDQ-B: Inflammatory Bowel Disease Questionnaire – B

Table 4. Mean General domain scores on the IBDQ-B questionnaire at different time points for the atorvastatin and placebo groups

	Intervention group (n = 32)	**Control group (n = 32)**	***P*-value**
Baseline (start of radiotherapy)	28 (28. 28)	28 (28. 28)	0.154
End of radiotherapy	28 (28, 28)	28 (28. 28)	0.790
Nadir (lowest score) during radiotherapy	28 (28, 28)	28 (24.5, 28)	0.553
3-month post radiotherapy	28 (28, 28)	28 (28. 28)	0.722
Change from baseline in IBDQ-B general scores			
End of radiotherapy	0 (0, 0)	0 (0, 0)	0.608
Nadir (lowest score) during radiotherapy	0 (0, 0)	0 (0, 3.5)	0.436
3-month post radiotherapy	0 (0, 0)	0 (0, 0)	0.380

IBDQ-B: Inflammatory Bowel Disease Questionnaire – B

Table 5. Incidence of patient-reported bowel symptoms by randomized group

	Intervention group (n = 32)	Control group (n=32)	*P*-value
Distension	2	4	0.391
Pain	6	8	0.545
Diarrhea	6	9	0.376
Urgency	3	1	0.302

Table 6. Detailed breakdown of toxicity grades by group

Phase	Intervention (n = 32)	Control (n = 32)	*P*-value
Week 1-2	2 (6.3%)	3 (9.4%)	0.642
Week 3-4	4 (12.5%)	5 (15.6%)	0.718
Week 5-6	6 (18.8%)	8 (25%)	0.544
Week 7-8	3 (9.4%)	4 (12.5%)	0.688
Post-treatment	1 (3.1%)	2 (6.3%)	0.554

Table 7. Comparison of grade ≥3 toxicities between groups

Symptom	Intervention (n = 32)	Control (n = 32)	*P*-value
Distension	0	0	NA
Pain	0	1 (3.1%)	0.313
Diarrhea	0	1 (3.1%)	0.313
Urgency	0	0	NA
Any Grade ≥3	0	2 (6.2%)	0.151

*Fisher's exact test

Table 8. Peak timing of toxicity by treatment phase

Phase	Intervention (n = 32)	Control (n = 32)	*P*-value
Week 1-2	2 (6.3%)	3 (9.4%)	0.642
Week 3-4	4 (12.5%)	5 (15.6%)	0.718
Week 5-6	6 (18.8%)	8 (25%)	0.544
Week 7-8	3 (9.4%)	4 (12.5%)	0.688
Post-treatment	1 (3.1%)	2 (6.3%)	0.554

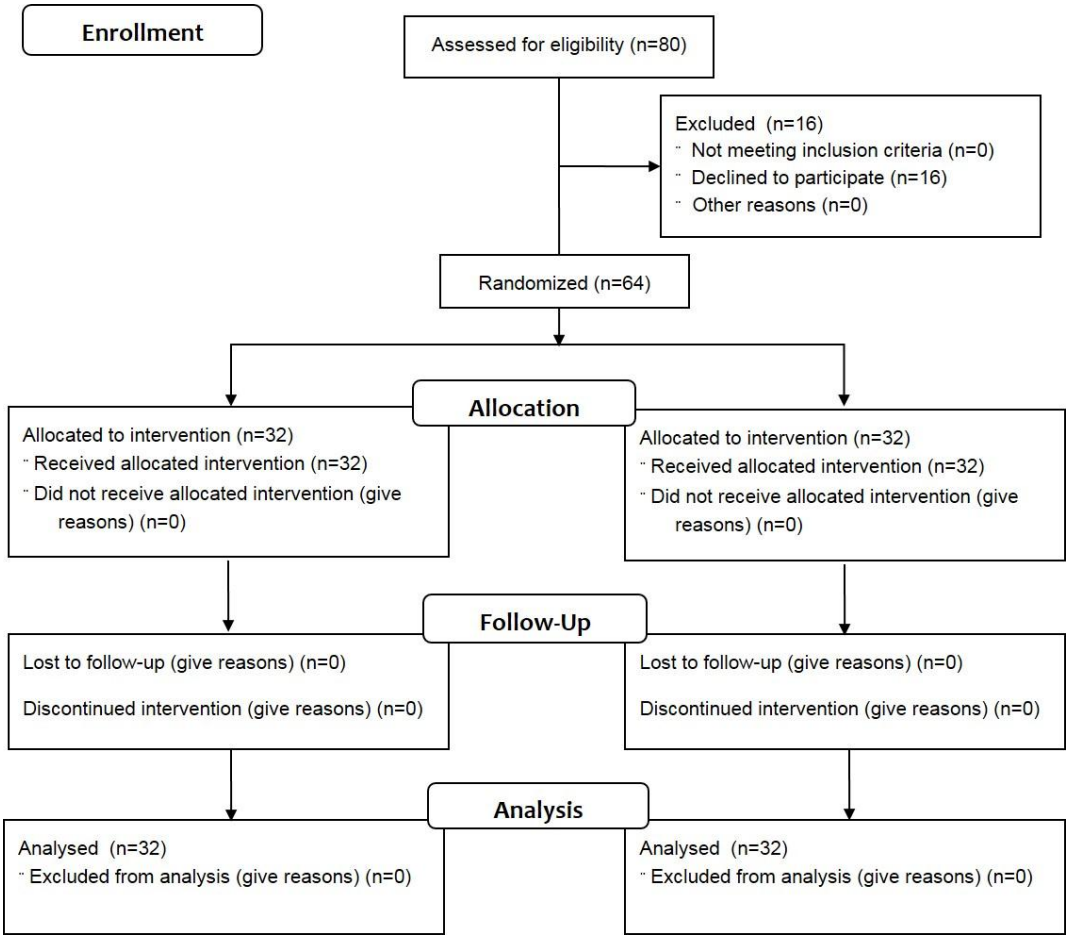

Figure 1. This figure shows the CONSORT diagram depicting patient flow through the trial.