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# Protective Effect of Amifostine on Radiotherapy-Applied Cardiovascular Tissue


## ABSTRACT

**Background:** The present study evaluates the protective effect of amifostine (AMI) on acute toxicity in large vessels and the heart in rats with radiotherapy (RT) applied to the thorax.

**Methods:** Twenty-one Wistar albino rats were randomly assigned to 3 groups: Alone RT (n = 7), amifostine plus RT (AMI+RT, n = 7), and control (n = 7) groups. The rats in the RT and AMI+RT groups received a single dose of 20 Gy radiation to the entire thorax. Prior to irradiation, AMI was administered intraperitoneally at a dose of 200 mg/kg, 30 minutes before the procedure. Five days after irradiation, the levels of p53, CD68, and COX in the vascular tissue (aorta) were measured, along with the levels of malondialdehyde (MDA) and glutathione (GSH) in the aortic and heart tissues.

**Results:** The results showed that the level of MDA significantly increased after irradiation, but GSH levels did not change ($P < .001$ and $P = 0.138$). Malondialdehyde levels were significantly reduced by AMI, and GSH levels increased ($P = .031$ and $P = .007$). When comparing the control group with AMI + RT, MDA and glutathione levels were similar ($P = .314$ and $P = .136$). Histopathological evaluation revealed increased cellular inflammation ($P = .002$) and vascular damage ($P = .015$) in aortic tissue after thoracic RT irradiation, but no difference in terms of myofibrosis ($P = .901$) in heart tissue.

**Conclusion:** AMI has a radioprotective and antioxidant effect against RT-induced cardiovascular toxicity.


**Keywords:** Amifostine, cardiovascular disease, prevention, radiotherapy

ORIGINAL INVESTIGATION

## INTRODUCTION

Mediastinal RT has been shown to reduce mortality and recurrence of thoracic malignancies (such as breast cancer and Hodgkin lymphoma). Thus, the survival rate of patients has gradually increased.[1,2] However, RT might potentially lead to RT-induced cardiovascular disease in the long term.[3] Cardiovascular toxicity has been the primary trigger of death in these patients, potentially accounting for one-quarter to one-third of total mortality.[4-6] Radiation-induced coronary artery disease has been one of the most active research arenas in the current literature. Lesions in the coronary arteries due to radiation generally tend to be more diffuse and involve the ostia of the coronary arteries.[7-9] Furthermore, radiation-induced damage might potentially occur in other large vessels. Previous studies have reported cases of aortic and carotid artery rupture following RT.[10]

Potential causes of RT-induced cardiovascular damage arise as accelerated atherosclerosis (at 8 Gy) and microvascular changes (at radiation doses of 8 Gy and 2 Gy, respectively).[11]

Amifostine (AMI) is a prodrug that is converted in vivo by alkaline phosphatase to the active cytoprotective sulfhydryl compound.[12] This substance has a protective effect on normal cells against the toxic effects of antineoplastic agents. It removes free radicals, binds hydrogen ions, and activated derivatives of the antineoplastic agent. Additionally, it has been demonstrated to exert important radioprotective effects on oral mucosa, lung, kidney, and bone tissues.[12-14]

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Apoptosis is an important regulatory mechanism that plays a central role in atherosclerosis and other vascular diseases.[15] The p53, CD68, and COX serve as inflammatory and apoptotic markers. The p53 has been harnessed as an indicator of DNA damage, while CD68 and COX have been used as indicators of vascular toxicity in histopathological evaluation.[16]

Additionally, malondialdehyde (MDA) and glutathione (GSH) have been utilized as indicators of oxidative stress in serum and tissues. Malondialdehyde is a by-product formed during lipid peroxidation, and its concentration is directly proportional to tissue damage associated with oxidative stress.[17] Glutathione is a critical enzyme involved in the detoxification of various reactive oxygen species that lead to oxidative myocardial damage.[17] The reduction of MDA, along with the increase of GSH, serves as an antioxidant factor.[18]

Based on the literature available, it was hypothesized that AMI might potentially have protective effects against radiation in large vascular tissue. The aim of this study is to evaluate the effectiveness of AMI in cardiovascular protection using histopathological and biochemical methods.

## METHODS

### Animals and Experimental Design

Prior to the study, the Institutional Animal Ethics Committee provided approval for the experimental procedures to be conducted on animals. A power analysis was performed before the study, and the minimum number of subjects was determined to be 7 mice for each group. Wistar rats were obtained from the experimental animal unit. The rats were fed standard mouse food and tap water freely, kept in groups in special cages with a mean temperature 21°C ± 2°C and mean humidity of 55% ± 2%. Twenty-one rats were randomly assigned to 3 groups, for the following treatments: Group 1: received irradiation alone (RT, n = 7) 1 mL/kg, intraperitoneal (i.p.) normal saline administered 30 minutes prior to irradiation (a single dose of 20 Gy). Group 2 received AMI and irradiation (AMI + RT, n = 7), with 200 mg/kg i.p. Amifostine administered 30 minutes prior to irradiation. Group 3 served as control (n = 7), with 1 mL/kg normal saline administered by i.p. injection 30 minutes prior to sham irradiation.

## HIGHLIGHTS

- Amifostine has a radioprotective and antioxidant effect against radiotherapy (RT)-induced cardiovascular toxicity.
- Pre-treatment with amifostine prior to irradiation resulted in increased levels of p53, CD68, COX and GSH and decreased levels of malondialdehyde.
- Histopathological evaluations indicated a reduction in inflammation and vascular damage.
- This study represents a significant contribution to the existing literature, as it is the first to demonstrate that amifostine may provide cardioprotective protection against mediastinal RT at the tissue level.

The experimental procedures were conducted on anesthetized rats using ketamine and xylazine (50 mg/kg body weight [BW] and 10 mg/kg BW, i.m.) during irradiation. The rats were monitored for 5 days by veterinary care personnel.

### Irradiation

Rats that received RT and AMI + RT were irradiated with a single dose of 20 Gy. The irradiation dose was delivered to the entire anterior mediastinum using a 3 cm × 4 cm single portal with 6 MV photons at a 1 cm depth and a 100 cm source-skin distance. The rats were anesthetized and then fixed to the 20 cm × 30 cm blue Styrofoam treatment bed in the prone position. Correct positioning of the fields was verified for each rat using a therapy simulator. Special dosimetry was applied for irregular areas. The dose uniformity across the field was ± 5%. The control group received an equivalent amount of irradiation in corresponding regions.

### Euthanasia

Euthanasia was performed 5 days after radiation therapy. Prior to euthanasia, the rats were anesthetized using a combination of ketamine and xylazine. Decapitation was performed for euthanasia. Histopathological and biochemical evaluations were performed by removing the aorta (as a great vessel) and the heart (including the right and left ventricles, interventricular septum, and pericardium).

### Histopathological and Biochemical Analysis

The samples were dehydrated, embedded in paraffin blocks, and serially sectioned (5 µm) before being stained with hematoxylin and eosin (H&E). The sections were examined under an Olympus BX51 Microscope (Olympus BX51, Tokyo, Japan) to determine the degree of inflammation in each layer of the ventricles.

Myocardial inflammation was graded on a scale of 0 to 3, with 0 indicating no inflammation, 1 indicating mild inflammation, 2 indicating medium inflammation, and 3 indicating severe inflammation. The degree of fibrosis in the myocardium of ventricles was assessed using a graded scale ranging from 0 to 4: 0 indicates no fibrosis, 1 indicates fibrosis in a small area, 2 indicates less than 5% area affected, 3 indicates 5%-10% area affected, and 4 indicates more than 10% area affected. Furthermore, vascular damage in the aorta was evaluated using a graded scale ranging from 0 to 3: 0 indicates no fibrosis, vascular adventitia thickness being 50% of the medial thickness; 1 indicates mild fibrosis, adventitia thickness equal to media thickness, 2 indicates medium fibrosis, with adventitia thickness twice the medial layer; and 3 indicates severe fibrosis, with adventitia thickness 3 times the medial layer.[19] The study examined the values of p53, CD68, and COX as inflammatory markers. The p53 antibody used in the study was the BioGenex DO7 clone, while the CD68 antibody was the Ventana Roche KP-1 clone, and the COX antibody was the Leica 4H12 clone.

Additionally, the levels of aortic and heart tissue MDA and GSH were evaluated as indicators of oxidative damage resulting from cardiac and vascular effects that develop after RT in the physiology laboratory. The tissue specimens were washed with a solution of cold 0.9% NaCl and stored

at −20°C until they were used for biochemical studies. The tissues were weighed separately, and then homogenized in 10 volumes of cold KCl using a potter-type homogenizer. Samples were then centrifuged at 8000 × g for 10 minutes at 4°C.

Levels of MDA, a marker of lipid peroxidation, in tissue and serum were determined using the thiobarbituric acid reactive derivatives method as previously established by Ohkawa et al,[20] GSH levels were determined by the Ellman method.[21] The protein content of the tissues was evaluated through the method of Lowry et al[22] Quantitative results were expressed as "nmol/mg protein."

### Statistical Analysis

Statistical assessments were conducted using TURCOSA statistical software (Turcosa Analytics Ltd Co, Türkiye, www.turcosa.com.tr). The mean and SD were employed to summarize the continuous variables. The frequency and percentage were utilized to summarize the categorical variables. The normal distribution assumption was assessed through the implementation of the Shapiro–Wilk test. The assessments were performed using a one-way analysis of variance (ANOVA) followed by a Tukey post-hoc test and Pearson chi-square test between the groups. The statistical significance level was established at $P < .05$.

The production of the submitted work did not make use of any artificial intelligence (AI)–assisted technologies, including large language models, chatbots, or image creators.

## RESULTS

Histopathological analyses were performed on 21 rats. No deaths occurred during the follow-up period. Biochemical analyses, including the count of aortic and heart tissue, and the levels of MDA and GSH, showed significant differences between the groups. The administration of AMI was observed to result in a reduction in MDA levels ($P = .031$) and an increase in GSH levels ($P = .007$) within the tissues, thereby demonstrating a protective effect. Table 1 summarizes the aortic, heart, and lung tissues for each group.

The rats were classified histopathologically, and intergroup statistical analysis was performed (Table 2). The combination of AMI and RT demonstrated a notable reduction in the impact of RT on inflammatory processes ($P = .002$) and vascular injury ($P = .015$) during the acute phase.

The ascending aortic tissue was subjected to histopathological staining. Figures 1-3 show COX staining, p53 and CD68 staining, and H&E staining, respectively.

## DISCUSSION

Cardiotoxicity is a significant adverse effect of RT. Studies aimed at mitigating cardiotoxicity associated with RT may offer potential methods. For this reason, the radioprotective efficacy of AMI on cardiovascular tissue was assessed. The key findings of this study are as follows: irradiation decreased p53, CD68, and COX levels and led to an increase in MDA levels. Pre-treatment with amifostine prior to irradiation resulted in increased levels of p53, CD68, COX and GSH and decreased levels of MDA. Histopathological evaluations indicated a reduction in inflammation and vascular damage. This study makes a substantial contribution to the extant literature, as it is the first to demonstrate that AMI may provide cardioprotective protection against mediastinal RT at the tissue level.

The RT group had lower levels of p53 and COX compared to the control group. In the AMI plus RT group, it was found that p53 and COX levels significantly improved but did not reach the levels of the control group. It has been demonstrated that AMI has positive effects on p53 and COX, but it does not fully recover RT-related damage. Further studies are needed to investigate additional treatment strategies.

**Table 1. Malondialdehyde and Glutathione Levels in Aortic, Lung, and Heart Tissues**

| | RT (group 1) | RT+ Amifostine (group 2) | Saline (group 3) | *P** -Groups 1 and 3 -Groups 1 and 2 |
|---|---|---|---|---|
| MDA aortic | 0.139 ± 0.016 | 0.123 ± 0.023 | 0.093 ± 0.012 | <.001 .031 |
| MDA heart | 0.448 ± 0.038 | 0.480 ± 0.074 | 0.527 ± 0.057 | .013 .482 |
| MDA lung | 0.961 ± 0.017 | 0.926 ± 0.031 | 0.806 ± 0.097 | .110 .402 |
| GSH aortic | 0.107 ± 0.024 | 0.179 ± 0.058 | 0.124 ± 0.028 | .198 .007 |
| GSH heart | 0.913 ± 0.132 | 1.038 ± 0.239 | 1.193 ± 0.227 | .018 .277 |
| GSH lung | 0.324 ± 0.079 | 0.310 ± 0.046 | 0.310 ± 0.090 | .949 .848 |

GSH, glutathione; MDA, malondialdehyde; RT, radiotherapy.
*P value generated from ANOVA test.

**Table 2. Comparison of Histopathological Evaluation of the Groups**

| | Group 1 RT n=7(%) | Group 2 RT+AMI n=7(%) | Group 3 Control n=7(%) | *P** |
|---|---|---|---|---|
| Inflammation | | | | .002 |
| 0 | 1 (14.28%) | 1 (14.2%) | 5 (71.42%) | |
| 1 | 2 (28.57%) | 6 (85.71%) | 2 (28.57%) | |
| 2 | 4 (57.14%) | 0 | 0 | |
| Myofibrosis | | | | .901 |
| 0 | 1 (14.28%) | 2 (28.57%) | 3 (42.85%) | |
| 1 | 2 (28.57%) | 3 (42.85%) | 2 (28.57%) | |
| 2 | 3 (42.85%) | 2 (28.57%) | 2 (28.57%) | |
| 3 | 1 (14.28%) | 0 | 0 | |
| Vascular damage | | | | .015 |
| 0 | 0 | 0 | 3 (42.85%) | |
| 1 | 4 (57.14%) | 4 (57.14%) | 4 (57.14%) | |
| 2 | 2 (28.57%) | 3 (42.85%) | 0 | |
| 3 | 1 (14.28%) | 0 | 0 | |

AMI, amifostine; n, number; RT, radiotherapy.
*Pearson chi-square test.

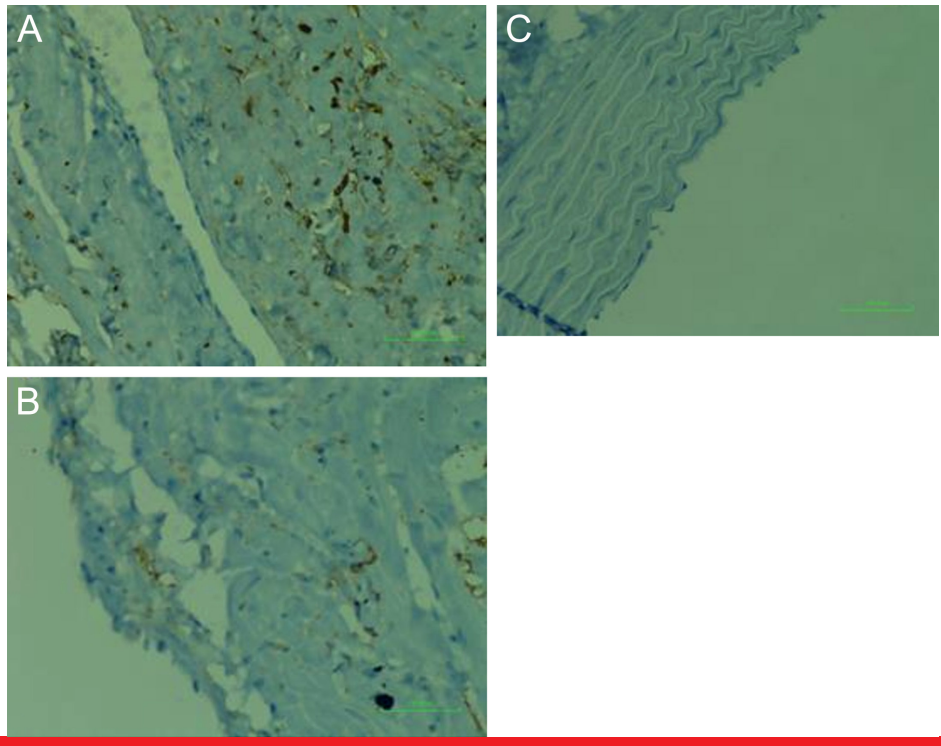


**Figure 1. Cox immunohistochemical staining (100×) at microscopy of ascending aortic tissue. A: Cox staining in group 1, inflammation stage 2, and vascular damage stage 1. B: Cox staining group 2, inflammation stage 1, and vascular damage stage 1. C: Cox staining group 3, inflammation stage 0, and vascular damage stage 0.**

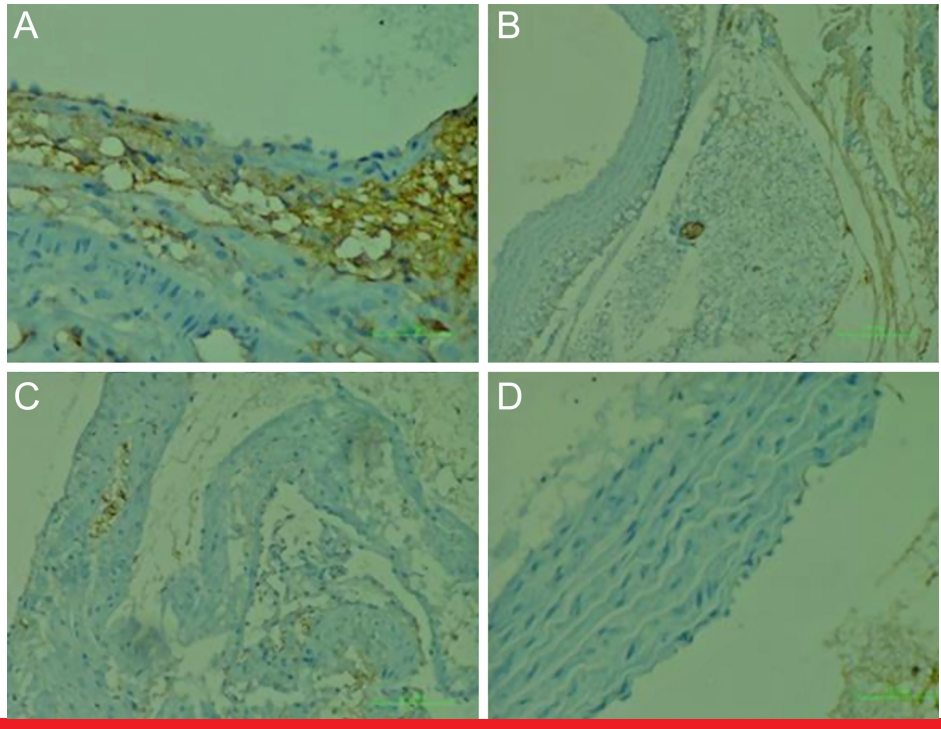


**Figure 2. CD68 and p53 immunohistochemical staining (100-200×) microscopy of ascending aortic tissue. Subendothelial histiocytes are stained. A: CD68 staining in group 1, inflammation stage 2, and vascular damage stage 2. B: p53 staining in group 1, inflammation stage 1, and vascular damage stage 1. C: CD68 staining in group 2, inflammation stage 1, and vascular damage stage 1. D: p53 staining in group 2, inflammation stage 0, and vascular damage stage 0.**

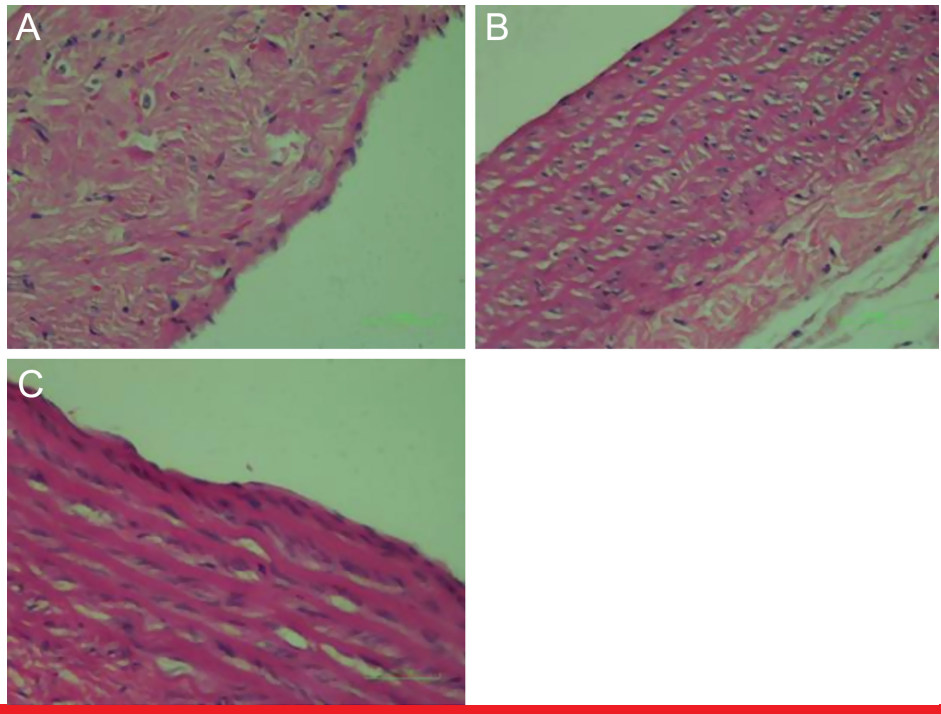


**Figure 3. Hematoxylin and eosin (H&E) immunohistochemical staining (200×) at microscopy of ascending aortic tissue. A: H&E staining in group 1, inflammation stage 2, and vascular damage stage 2. B: H&E staining group 2, inflammation stage 1, and vascular damage stage 1. C: H&E staining group 3, no inflammation and vascular damage stage 0.**

In terms of CD68 levels, the RT alone group had lower levels compared to the control group. In the AMI + RT group, CD68 levels were similar to those of the control group. Based on these results, it can be inferred that CD68 is released as an antioxidant factor to protect against vascular damage. Additionally, AMI has a protective impact against the adverse effects of RT on vascular tissue by increasing CD68 levels.

The results of the histopathological evaluation demonstrated that inflammation was significantly higher in the RT group compared to the control group, with predominantly grade 2 damage observed. In contrast, the AMI group showed no grade 2 damage, resembling the control group. As expected, given the late onset of myofibrosis, all groups exhibited similar results. However, the AMI group showed no grade 3 damage, similar to the control group. The RT group displayed significantly higher grades of vascular damage (grades 2 and 3) compared to the control group. However, the addition of amifostine prevented grade 3 damage, bringing the AMI group in line with the control group. Amifostine reduced the destructive impact of RT on heart and aortic tissues, particularly preventing the inflammation and vascular damage. RT has been demonstrated to elicit tissue destruction through the acceleration of atherosclerosis and microvascular damage, which might be attributable to the increased inflammation and oxidative stress that it induces. In this study, the RT + AMI group exhibited a reduction in advanced inflammation due to AMI's antioxidant activity. Similarly, the incidence of vascular damage was found to be lower. Given that the effect on myofibrosis manifested during the chronic phase, no change was observed in the acute phase in the present study. Gürses et al[23] similarly reported that RT causes heart diseases through inflammation, necrosis, and vascular damage mechanisms. Our study recommends a treatment that minimizes this damage.

As anticipated, tissue damage associated with RT led to elevated levels of aortic and heart tissue MDA. However, it was observed that MDA levels in the AMI group were similar to those in the control group. This suggests that the protective effect of AMI against oxidative stress and tissue damage may have contributed to this outcome. Previous studies have also shown the protective effects of AMI on tissues. However, this study is the first to demonstrate the cardiovascular effects in subjects undergoing mediastinal RT.[24] In aortic tissue, MDA levels were significantly elevated in the RT group compared to the control group, indicating radiation-induced damage. The RT group also showed higher MDA levels compared to the AMI group, but the increase was less pronounced in the AMI group, highlighting the protective effect of amifostine. Surprisingly, in cardiac tissue, MDA levels were significantly lower in the RT group compared to the control group, and similar to the AMI group. In lung tissue, MDA levels showed a non-significant increase in the RT group compared to the control group and were comparable to those in the AMI group. Biochemical evidence of RT-induced damage was observed exclusively in aortic tissue, where amifostine demonstrated a protective effect. Although the AMI group provided partial protection in lung tissue, this effect did not reach statistical significance.

The production of reactive oxygen species (ROS) can potentially deplete the endogenous antioxidant system, leading to oxidative damage. In cellular defense against ROS, GSH

serves as the first line of cellular defense due to its ability to strongly decompose superoxide anions and hydrogen peroxide.[25] However, in this study, GSH activity did not increase in the rat heart tissue treated with RT compared to control rat heart tissue, possibly due to insufficient endogenous antioxidant mechanisms. The increase in GSH levels in the AMI + RT group supports the protective impact of GSH against oxidative stress.[26] In aortic tissue, GSH levels were similar between the RT and control groups but significantly higher in the AMI group, reflecting a protective effect. In cardiac tissue, GSH levels were significantly reduced in the RT group compared to the control group. While GSH levels were higher in the AMI group compared to the RT group, the increase was not statistically significant. In lung tissue, GSH levels were similar across all groups, with no significant differences observed. The protective effect of amifostine was primarily evident in aortic tissue and to a limited extent in cardiac tissue. No biochemical effect was observed in lung tissue.

Acute cardiotoxicity can be either transient or permanent and may occur during or shortly after completion of RT. However, coronary artery disease and heart failure typically arise long after RT. The magnitude and extent of cardiovascular damage are strongly associated with the dose of radiation applied to the mediastinum.[11] In the present study, the 20 Gy dose was selected for mediastinal RT in order to utilize high doses (≥10 Gy) in the general treatment of cancer[3,27,28] and to examine the acute effects of such doses in particular.

Recent publications suggest that stereotactic body radiation therapy (SBRT) may be effective in treating ventricular tachycardia (VT) that is difficult to access (AVR+MVR patients), refractory to medical therapy, or advanced hypertrophic myocardial tissue.[29,30] There is no specific recommended dose of RT, but doses of ≥25 Gy have been used. When considering the results of this study, it appears that the use of AMI in these new treatment plans may help prevent damage to healthy tissue in the microvascular or aorta of patients. This suggests that it could be useful in preserving normal cardiac and mediastinal tissues.

Although studies have demonstrated that AMI reduces the cardiotoxicity of chemotherapeutic agents, no study has yet evaluated the effectiveness of AMI on mediastinal RT-induced cardiovascular toxicity.[31] This study suggests that pretreatment with AMI before thorax RT may increase the antioxidant mechanisms, leading to a significant reduction in cardiovascular toxicity. Biochemical and histopathological analyses demonstrated that radiation-induced damage was most evident in aortic tissue. Amifostine provided significant protection, particularly in reducing MDA levels and vascular damage in aortic tissue. Additionally, amifostine appeared to mitigate cardiac inflammation and prevent severe vascular damage. No substantial protective effects were observed in lung tissue.

### Study Limitations

There are also a variety of limitations. Firstly, the impact of further and delayed doses of RT was not investigated, and different doses may have varying effects on cardiovascular tissue. Second, the long-term effects of RT were not evaluated. Additionally, other antioxidants and apoptotic markers were not evaluated in this study.

## CONCLUSION

Amifostine may provide protection against acute cardiovascular toxicity associated with single fraction irradiation. Therefore, it is useful to examine the effects of in-vivo administration of AMI in cancer patients receiving RT, with the expectation of eliminating RT-induced cardiovascular toxicity. These results are preliminary but exciting for future research. Combination therapy using AMI with angiogenic pharmaceutical agents could be explored as an optimal strategy for maintaining and restoring vascular quality against the toxic impact of RT.

**Ethics Committee Approval:** This study protocol was reviewed and approved by the Institutional Animal Ethics Committee (TUTF-HDEK/2016). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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**Author Contributions:** All of the authors declare that they have participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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