ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2026.08769

Hamidiye Med J

# Radiotherapy-Induced Thymus Histopathological Alterations at Different Dose Rates: The Protective Role of Melatonin

## Farklı Doz Hızlarında Radyoterapiye Bağlı Timus Histopatolojik Değişiklikleri: Melatoninin Koruyucu Rolü

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ABSTRACT

**Background:** This study aimed to investigate the histopathological alterations in thymus tissues induced by single-dose radiotherapy (RT) delivered at different dose rates using flattening filter (FF) and FF-Free (FFF) beams, and to assess the potential protective effects of melatonin (MEL).

**Materials and Methods:** Forty-eight female Sprague–Dawley rats were randomly assigned to six groups (n = 8): control (G1), MEL (G2), FF (G3), FF + MEL (G4), FFF (G5), and FFF + MEL (G6). RT was administered as a single 16 Gy dose using a 6 MV photon source. The dose rate was set at 600 MU/min for FF beams and 1400 MU/min for FFF beams. MEL (10 mg/kg, intraperitoneal) was administered prior to irradiation. All animals were sacrificed 48 hours after RT. Histopathological assessments were performed using hematoxylin & eosin and toluidine blue staining.

**Results:** Groups G1 and G2 exhibited normal thymic morphology, with intact corticomedullary boundaries and predominantly granulated mast cells. In contrast, G3 and G5 exhibited significant histopathological damage scores, characterised by reduced thymocyte density, disrupted lobular architecture, vacuolar degeneration, and increased apoptotic bodies. Mast-cell degranulation was minimal in G3 but significantly elevated in G5. The MEL-treated groups (G4 and G6) exhibited significant morphological improvements, characterised by the preservation of cortical-medullary organisation and an increased number of granulated mast cells. Although damage scores decreased significantly, only G6 showed a significant reduction in mast cell degranulation compared with G5.

**Conclusion:** A single dose of RT induced histopathological changes in thymic tissue, whereas MEL administration significantly attenuated these changes. These findings suggest that MEL may be a promising protective agent for reducing RT-related side effects and that FF and FFF beams exhibit similar biological effects on healthy tissues.

**Keywords:** Radiotherapy, melatonin, histopathology, thymus, mast cell

ÖZ

**Amaç:** Bu çalışma, timus dokularında Flattening Filter (FF) ve FF-Free (FFF) ışınları kullanılarak farklı doz hızlarında uygulanan tek doz radyoterapinin (RT) neden olduğu histopatolojik değişiklikleri araştırmak ve melatoninin (MEL) potansiyel koruyucu etkilerini değerlendirmek amacıyla yapılmıştır.

**Gereç ve Yöntemler:** Kırk sekiz dişi Sprague–Dawley sıçanı rastgele altı gruba (n = 8) ayrıldı: kontrol (G1), MEL (G2), FF (G3), FF + MEL (G4), FFF (G5) ve FFF + MEL (G6). RT, 6 MV foton kaynağı kullanılarak tek bir 16 Gy doz olarak uygulandı. Doz oranı, FF ışınları için 600 MU/dk ve FFF ışınları için 1400 MU/dk olarak ayarlandı. MEL, ışınlamadan önce 10 mg/kg dozunda intraperitoneal olarak uygulandı. Tüm hayvanlar RT sonrası 48 saat sonra sakrifiye edildi. Histopatolojik değerlendirmeler hematoksilen & eozin ve toluidin mavisi ile boyandı.

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**Received:** 12.12.2025 **Accepted:** 20.02.2026 **Epub:** 22.05.2026

**Cite this article as:** Erdem E, Karip BZ, Aras S. Radiotherapy-induced thymus histopathological alterations at different dose rates: the protective role of melatonin. Hamidiye Med J.

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ÖZ

**Bulgular:** G1 ve G2 grupları, sağlam kortikal-medüller sınırları ve ağırlıklı olarak granülasyonlu mast hücreleri ile normal timus morfolojisi sergiledi. Buna karşın, G3 ve G5 grupları, timosit yoğunluğunda azalma, lobüler mimarinin bozulması, vakuolar dejenerasyon ve artmış apoptotik cisimler ile karakterize edilen önemli histopatolojik hasar skorları sergiledi. Mast hücre degranülasyonu G3'te minimum düzeydeyken, G5'te önemli ölçüde artmıştı. MEL ile tedavi edilen gruplar (G4 ve G6), kortikal-medüller organizasyonun korunması ve granül mast hücrelerinin sayısında artış ile karakterize edilen önemli morfolojik iyileşmeler sergiledi. Hasar skorlarında önemli bir azalma görülürken, sadece G6, G5 ile karşılaştırıldığında mast hücre degranülasyonunda önemli bir azalma gösterdi.

**Sonuç:** Tek doz RT, timus dokularında benzer histopatolojik değişikliklere neden olurken, MEL uygulaması bu değişiklikleri önemli ölçüde azalttı. Bu bulgular, MEL'in RT'ye bağlı yan etkileri azaltmak için umut verici bir koruyucu ajan olabileceğini ve FF ve FFF ışınlarının sağlıklı dokular üzerinde benzer biyolojik etkiler sergilediğini göstermektedir.

**Anahtar Kelimeler:** Radyoterapi, melatonin, histopatoloji, timus, mast hücresi

## Introduction

Cancer is a disease that profoundly impacts both life expectancy and quality of life. Cancer treatment is a multifaceted approach, incorporating surgical intervention, chemotherapy, and radiotherapy (RT). RT remains widely used in cancer treatment. Approximately 60% of cancer patients receive radiation therapy as part of their treatment regimen (1). RT, an effective and safe method used in various cancer treatments, targets tumor cells and induces cell death through mechanisms involving DNA damage and oxidative stress. However, it is essential to note that healthy tissues in proximity to the tumor may also be subjected to the deleterious effects of radiation during the course of treatment. Organs of the immune system are susceptible to radiation, and such damage can precipitate secondary complications during treatment. Radiation therapy has been observed to decrease lymphocyte count. Furthermore, this treatment has been shown to damage stromal cells, particularly those of the thymus. In addition, it has been shown to alter extracellular signaling factors, thereby inhibiting the proliferation of T-cell precursors (2). The objective of this treatment is to deliver the maximum permissible dose to the tumor while minimizing damage to surrounding healthy tissue.

The thymus is a central lymphoid organ where T lymphocytes mature and immune tolerance develops. This organ, which is most active during early life, plays a critical role in shaping the adaptive immune response and defending the organism against infections and tumors. The histopathological effects of radiation on thymic tissue have been reported as follows: apoptosis of thymocytes; damage to stromal and epithelial cells; disruption of immune tolerance mechanisms; and reduced functional support of the thymic microenvironment (3). Thus, the utilisation of antioxidants has emerged as a pivotal strategy to counteract RT-induced oxidative damage and to safeguard the integrity and function of thymic tissue.

Antioxidants have been utilized to mitigate the adverse effects of RT (4). Numerous studies have examined the effects of various compounds, including antioxidants, vitamin supplements, and herbal extracts, all of which have been shown to protect against oxidative stress (5). Radioprotective agents such as melatonin (MEL) have been used to minimize radiation-induced tissue damage (6). MEL, a potent antioxidant, has been shown to neutralize endogenous hydroxyl radicals induced by radiation. It has been demonstrated to exhibit anti-inflammatory and anti-apoptotic properties, thereby preventing oxidative stress. This approach has been demonstrated to mitigate the deleterious effects of radiation on healthy tissues (7,8).

Advancements in RT have led to the development of flattening filter-free (FFF) beam technology, which has become a viable alternative to devices using FF. This technological advancement has enabled the instantaneous attainment of elevated dose rates and a substantial reduction in treatment duration (9).

A substantial body of research has been conducted as *in vitro* studies that systematically compare traditional low-dose rapid FF radiation and high-dose rapid FFF radiation in various cancer cell lines (6,10). However, the extant literature lacks *in vivo* research that adequately elucidates the protective effect of MEL against radiation-induced cell damage caused by FF and FFF beams in healthy tissues outside the tumor volume, such as the thymus. Consequently, the investigation of histopathological changes in thymus tissue after RT in healthy rats, as well as the potential protective effects of MEL administration on these changes, constitutes a significant area of research. In this study, the effects of single-dose FF and FFF beams on the head-and-neck regions of healthy Sprague–Dawley rats were investigated. The protective effects of MEL administration against RT-induced damage in thymic tissue were evaluated using histopathological methods; dose-rate effects varied across experimental groups.

## Materials and Methods

### Animal Care

Forty-eight female Sprague–Dawley rats, with an average weight of 250 ± 20 g, were observed under standard conditions (temperature 20 ± 10 °C, humidity 60 ± 10%, and a 12-hour light/12-hour dark cycle)in accordance with established protocols.

This study was conducted following approval by the Yeditepe University Experimental Research Center Ethics Committee (approval number: 724, dated: 13.02.2019). The study was conducted exclusively on laboratory animals and did not involve human subjects; therefore, informed consent was not required.

### Experimental Design and MEL Administration

The MEL dose and administration method were determined from previous biological studies demonstrating MEL's antioxidant effects in experimental rat models (6,11). Forty-eight rats were randomly divided into six groups (n = 8). A detailed overview of the experimental design and RT dose rates is provided in Table 1.

### RT Application

General anesthesia was administered to all rats except those in the control group, using 80 mg/kg/intraperitoneal ketamine and 5 mg/kg/intraperitoneal xylazine. Before RT, the subjects were placed in a supine position on a plexiglass tray. A single dose of 16 Gy was delivered to the head and neck regions of rats using 6 MV X-rays (Varian Trilogy), following experimental parameters reported in the literature for FF at 400 MU/min and FFF at 1400 MU/min. The source-to-axis distance was set to 100 centimeters (cm). Furthermore, a 10-mm-thick, water-equivalent Superflab bolus was placed in the RT field to balance the depth-dose distribution before irradiation (9).

### Histopathological Analyses

Forty-eight hours after RT, the rats were anesthetized with 80 mg/kg, intraperitoneal ketamine and 20 mg/kg, intraperitoneal xylazine, then euthanized by exsanguination. Samples were fixed in neutral-buffered formalin and subsequently processed using routine procedures for paraffin embedding. Sections with a thickness of 3 µm were obtained using a Microm HM325 microtome (Thermo Scientific, Germany). For morphological evaluation, the sections were stained with hematoxylin & eosin. The severity of tissue damage was determined by evaluating lesions in at least 10 distinct regions of each sample, based on the observed morphological alterations. Subsequently, comparisons were made between groups based on these scores (12). Toluidine blue staining was employed to visualize mast cell morphology within the tissue. The sections were examined for the presence of mature granulated and degranulated mast cells. At ten-section intervals, five distinct fields per section were assessed at ×400 magnification by two blinded observers. Mast cell quantification was performed by counting the number of cells per unit area (13,14).

### Statistical Analysis

The normality of data distribution was assessed using the Shapiro–Wilk test, and the homogeneity of variances was evaluated with Brown–Forsythe's test. After assessing these assumptions, group comparisons were performed using either Brown–Forsythe–corrected one-way analysis of variance (ANOVA) or standard one-way ANOVA. For post-hoc analyses, Tukey's test was applied when variances were equal, whereas Dunnett's T3 test was used when variances were unequal. All data are presented as mean ± standard deviation, and a p-value <0.05 was considered statistically significant. All statistical analyses were conducted using GraphPad Prism software (Version 8.4.2; GraphPad Software, San Diego, CA, USA).

**Table 1. Experimental design and treatment protocols of the study groups.**

| Group | Description | Treatment details |
|---|---|---|
| G1: control group | Animals were monitored without any intervention. | No treatment administered. |
| G2: MEL only group | Used to evaluate the effects of MEL alone. | Intraperitoneal MEL (10 mg/kg). |
| G3: FF group | Received RT at a low dose rate. | 16 Gy RT at 400 MU/min (low dose rate). |
| G4: FF + MEL group | Used to assess the combined effects of MEL and low–dose-rate RT. | Intraperitoneal MEL (10 mg/kg), followed 15 min later by 16 Gy RT at 400 MU/min. |
| G5: FFF group | Received RT at a high dose rate. | 16 Gy RT at 1400 MU/min (high dose rate). |
| G6: FFF + MEL group | Used to evaluate the interaction between MEL and high–dose-rate RT. | Intraperitoneal MEL (10 mg/kg), followed 15 min later by 16 Gy RT at 1400 MU/min. |

FFF, Flattening Filter-Free; MEL, melatonin; RT, radiotherapy.

## Results

The general morphological structure of the thymus was within healthy limits in groups G1 and G2. The boundaries between the cortex and medulla were distinct. The cortex showed a dense lymphocytic structure, while the medulla had a more open, regular appearance. No significant thickening or cellular infiltration was observed in the capsules or interlobular septa (Figure 1). Mast cells were observed to be concentrated in the perivascular area of the interlobular septa. The majority of the samples were morphologically intact, with granules preserved (Figure 2).

A substantial degree of histopathological damage was identified in the G3 and G5 groups. In both groups, a decrease in thymocyte density and a disruption of lobular architecture were observed in the cortical region. Vacuolization and apoptotic bodies were observed, accompanied by a significant loss of lymphocytes. Despite partial preservation of the medulla's structural integrity, pronounced edema was observed (Figure 1). The G3 group exhibited a significantly higher damage score compared with the G1 and G2 groups ($p < 0.001$) (Figure 3). The damage scores of the G5 group were also significantly higher than those of the G1 and G2 groups ($p < 0.001$) (Figure 3). No statistically significant difference was found between the damage scores of the G3 and G5 groups; both groups exhibited similar levels of damage (Figure 3). The results indicated a dec rease in the number of mast cells in the G3 and G5 groups compared to the G1 and G2 groups. Mast cells in the monitored G3 and G5 groups were predominantly in the degranulated phase (Figure 2). Granular mast cell counts were similar in the G3 and G5 groups, but they were lower than in the G1 and G2 groups. The degranulation rate in the G3 group was similar to that observed in the G1 and G2 groups (Figure 3). The degranulation rate in the G5 group was significantly higher than in the G1 and G2 groups ($p < 0.001$) (Figure 3). The G4 and G6 groups exhibited damage scores that were significantly lower than those observed in the G3 and G5 groups (Figure 3; $p < 0.001$, $p < 0.01$). Necrotic areas were less extensive, and cellular integrity was better preserved. The boundaries between the cortex and medulla were distinct (Figure 1). Histopathological analysis of mast cells in the G4 and G6 groups revealed no disruption and showed a regional distribution (Figure 2). Granule-intact cells were observed at a higher frequency than in the G3 and G5 damage groups, although the difference was not statistically significant (Figure 3). The degranulation rate in the G4 group showed a trend comparable to that observed in the G3 group. However, the G6 group demonstrated a statistically significant decrease compared with the G5 group (Figure 3; $p < 0.001$).

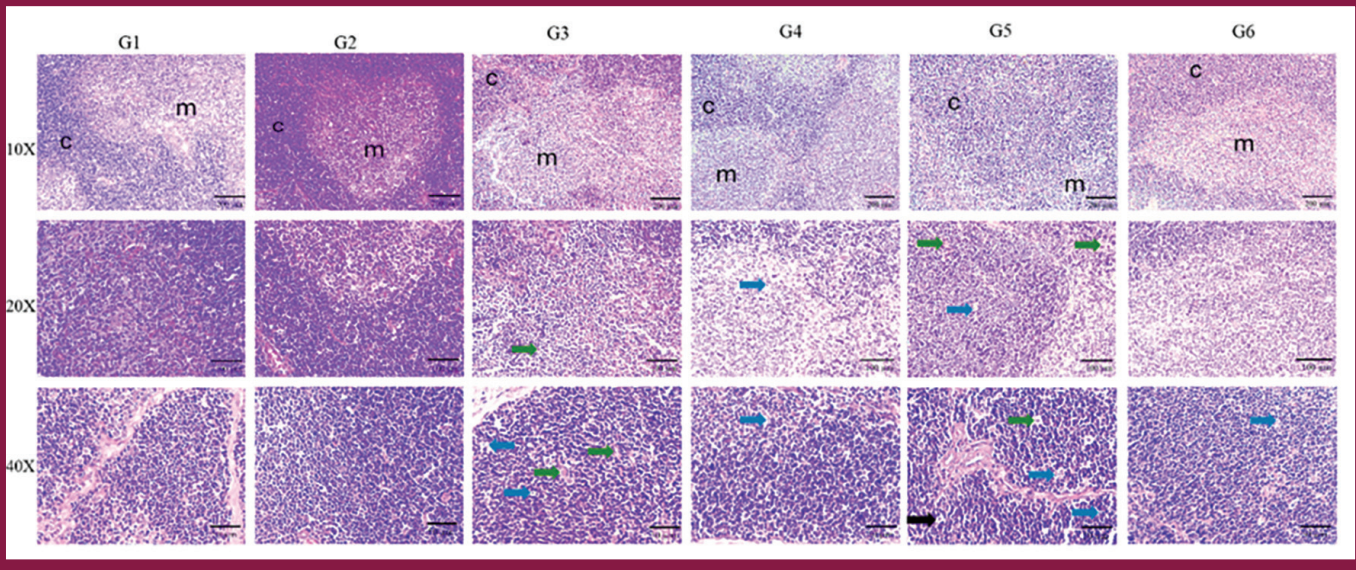



**Figure 1.** Histopathological evaluation of thymus tissue samples stained with hematoxylin & eosin. Samples from six experimental groups (G1–G6) are presented at 10×, 20×, and 40× magnifications. The micrographs show histopathological findings, including macrophages (black arrows), apoptotic bodies (blue arrows), and areas of necrosis (green arrows). Scale bars correspond to each magnification level.

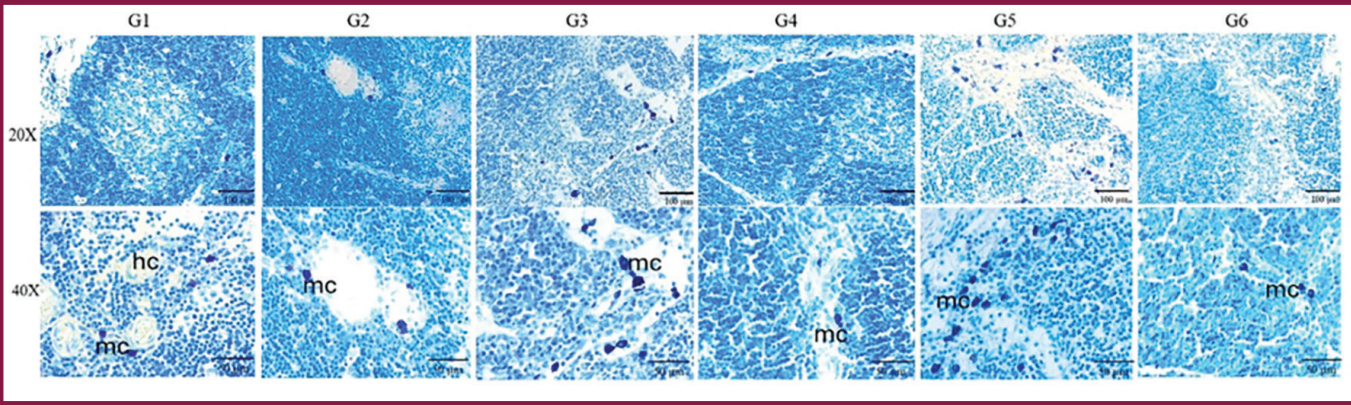



**Figure 2.** Histopathological evaluation of thymic tissue stained with toluidine blue presented at 20× and 40× magnifications (top row: 20×; bottom row: 40×). The micrographs depict key histological features of the thymus, including hc and mc. Scale bars correspond to the respective magnification levels.
*hc, Hassall's corpuscles; mc, mast cells.*

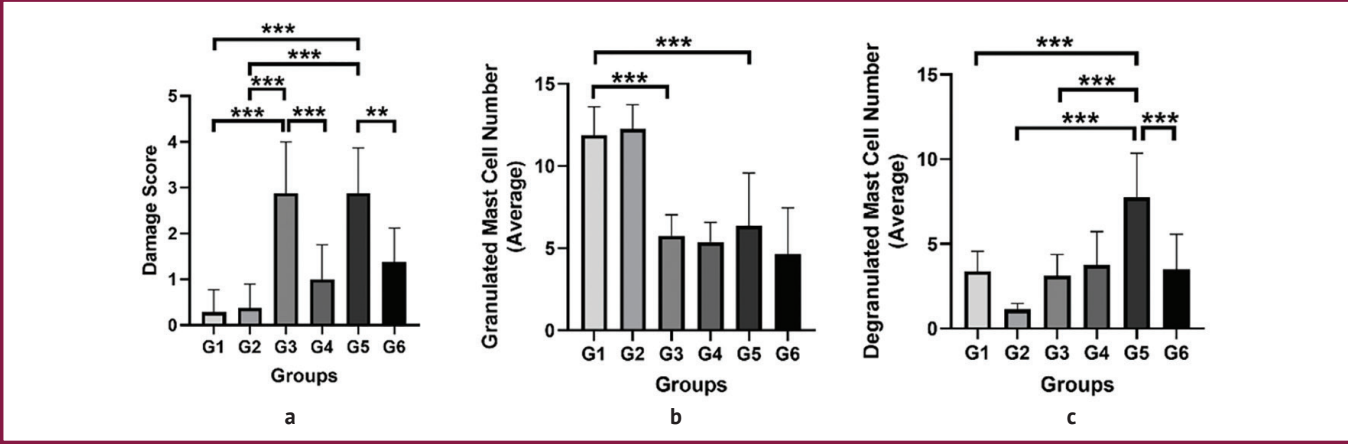



**Figure 3.** (a) Histopathological damage score comparisons among experimental groups. Significant differences between groups are indicated as **p < 0.01; ***p < 0.001. (b) Histopathological granulated mast cell count comparisons among experimental groups. Significant differences between groups are indicated as ***p < 0.001. (c) Histopathological degranulated mast cell count comparisons among experimental groups. Significant differences between groups are indicated as ***p < 0.001.

## Discussion

RT is an essential part of modern cancer treatment. Although it increases survival rates, it may also cause adverse effects in healthy tissues (15). In RT applications, dose rate planning aims to control side effects (16,17). In our study, we examined histopathological changes in healthy thymus tissue induced by RT protocols delivered at different dose rates using a single-dose regimen, as well as the protective effects of MEL treatment. The thymus is particularly susceptible to ionizing radiation because its thymocyte populations exhibit rapid proliferative activity and its stromal cells are radiosensitive (2,18). A study emphasized that lymphocytes are among the cell populations in the body most sensitive to ionizing radiation and that significant losses can be observed even at low-to-moderate doses (2). Similarly, Deng et al. (19) demonstrated that ionizing radiation in the thymus leads to marked increases in apoptosis and thymocyte loss. In comparisons of irradiation models, various studies have reported that the FFF mode, owing to its higher dose rate compared to the classical FF mode, may lead to differences in biological efficacy despite similar physical doses. It has been suggested that the dose distribution and dose-rate characteristics of FFF photon beams may alter DNA damage accumulation, repair dynamics, and the cellular stress response by shortening cellular exposure time (20-22).

In FFF dose-planned treatments, the increased dose rate reduces irradiation time, thereby shortening the time window available for cells to repair DNA damage. Consequently, reports indicate that both tumor and normal tissue responses differ from those observed with conventional FFF dose-planned treatments (20-24). Babayan et al. (23) and Terashima et al. (24) have highlighted not only dosimetric but also potential radiobiological differences between FF and FFF beams. They have reported that high-dose-rate FFF beams may increase cellular damage under certain conditions. In our study, damage characterized by decreased thymocyte density, vacuolization, pyknotic nuclei, increased apoptosis, and increased necrotic areas was also observed in the G3 and G5 groups. The observed damage confirms the expected pattern of injury triggered by ionizing radiation in the thymus. These findings support the notion that radiation causes both DNA breaks that directly affect thymocytes and secondary effects, such as loss of thymic stromal cells (3,19).

The literature on mast cell behavior following radiation exposure indicates that a mast cell can respond differently depending on radiation dose and dose rate, the cell's activation state, and the microenvironment to which it is exposed. Irradiation of dermal tissue has been shown to increase mast cell degranulation and tryptase release, which are essential components of the local inflammatory response and tissue reactions (25,26). Blirando et al. (27) reported that mast cells in the intestinal tissue are affected in both the acute and late phases following irradiation; mast cell hyperplasia and changes in the mediator profile can vary depending on the tissue and timing. Joo et al. (28) reported that low-dose ionizing radiation triggers mast cell degranulation and that this degranulation can increase under certain conditions. These findings reveal that mast cells not only change in number (increasing or decreasing), but also respond functionally (e.g., mediator release, granule discharge) in a manner sensitive to radiation dose and dose rate. In our study, although we did not observe a significant difference in mast cell count or degranulation in the G3 group, the G5 group showed a decreased granular mast cell count and a significantly increased degranulation rate. This finding suggests that mast cells may be a cellular target sensitive to changes in dose rate. The relatively higher damage score in our G5 group is consistent with the literature. In this context, it is thought that the high dose-rate used in FFF mode may have triggered a stronger acute stress response and increased mediator release in immune cell populations, including mast cells. The high dose rate applied using FFF beams may have led to exceeding the threshold for mast cell degranulation by shortening the cells' exposure time, even at the same physical dose, due to acute oxidative stress. In contrast, the lower instantaneous dose rate in FF mode may have limited the degranulation rate by allowing mast cells to partially adapt to this stress (20,28). These results demonstrate that the biological efficacy of FFF irradiation may vary with dose rate not only in tumor tissue but also in immune cells in healthy tissue, such as mast cells, and that mast cells may be a biomarker to consider in FFF-based protocols (20,28).

MEL treatment has been reported to ameliorate ionizing radiation-induced damage. It has been reported to protect normal tissues from radiation damage by both strengthening antioxidant defenses and scavenging free radicals (5,29-31). Experimental studies have shown that MEL can protect mast cells from chemically induced cytotoxicity and that mast cells synthesize it to modulate the immune response (32). It is thought to prevent uncontrolled mast cell degranulation by supporting mast cell stability through its free radical-scavenging effect (33,34). Mao et al. (31) reported that it maintained the morphological integrity of thymus tissue. Kvetnoy et al. (33) and Aliasgharzadeh et al. (35) demonstrated that MEL supplementation after irradiation increased mast cell counts and reduced mast cell degranulation. In our study, thymus tissue damage scores decreased in the G4 and G6 groups that received exogenous MEL compared with the damage group. Furthermore, the administration of MEL in both the G3 and G5 groups reduced mast cell counts, bringing them closer to control levels. While degranulation was elevated in the G5 group, it decreased markedly in the G6 group. In this context, MEL exhibited a radioprotective effect in the G5 group, indicating that its efficacy is evident under the corresponding dose-rate conditions. Additionally, degranulation counts differed significantly between the G3 and G5 groups, indicating a clear distinction between FF and FFF irradiation modalities. Thus, our results demonstrate that dose rate is associated with both damage to thymic tissue morphology and differences in mast-cell differentiation. They also reveal MEL's potential to rebalance this response at a functional level.

The present study examined only the acute effects of RT administered as a single dose and at different dose rates. While the mast cell counts and degranulation profiles determined in the study provided important biological clues, the underlying molecular mechanisms (such as oxidative stress markers, cytokine profiles, DNA damage, and repair pathways) were not examined in detail. Future studies should employ more comprehensive protocols incorporating a range of dose rates. Furthermore, these studies should include follow-up of late-phase effects and biochemical analyses. The purpose of these analyses would be to elucidate the mechanisms underlying oxidative stress and DNA repair.

## Conclusion

This study demonstrates that single-dose RT induces significant damage to healthy thymic tissue and that the extent of this damage is influenced by the dose rate. Despite identical physical doses, high-dose-rate irradiation delivered in the FFF mode resulted in more pronounced thymocyte loss, apoptosis, and mast cell degranulation compared with the conventional FF mode. MEL administration attenuated tissue injury and modulated mast cell responses, and its protective effect was particularly evident under high-dose-rate FFF conditions. These findings highlight the biological relevance of dose rate in RT and support the potential role of MEL as a radioprotective agent.

### Ethics

**Ethics Committee Approval:** This study was conducted following approval by the Yeditepe University Experimental Research Center Ethics Committee (approval number: 724, dated: 13.02.2019).

**Informed Consent:** Informed consent was not required.

### Footnotes

### Authorship Contributions

Concept: E.E., S.A., Design: E.E., S.A., Data Collection or Processing: E.E., B.Z.K., S.A., Analysis or Interpretation: E.E., B.Z.K., S.A., Literature Search: E.E., B.Z.K., S.A., Writing: E.E., B.Z.K., S.A.

**Conflict of Interest:** No conflict of interest was declared by the author(s).

**Financial Disclosure:** The author(s) declared that this study received no financial support.

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