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Effects of timing in the applications of radiotherapy after transverse rectus abdominis musculocutaneous flap in rats

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► ***Original article***

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ABSTRACT

***Background*:** The present study aimed to investigate flap status in relation to the timing of radiotherapy (RT) in an experimental rat model of irradiated transverse rectus abdominis musculocutaneous (TRAM) flap. ***Materials and Methods*:** Fifty-six adult male Sprague-Dawley experiments were separated in seven groups in terms of flap surgery and RT. The groups comprised sham group, control (Ctrl) group, RT group, and RT plus surgery (RT+Surg) group, which was further separated in four groups depending on the timing of postoperative RT as RT+Surg-10 (RT on postoperative 10th day), RT+Surg-20 (RT on postoperative 20th day), RT+Surg-30 (RT on postoperative 30th day), and RT+Surg-40 (RT on postoperative 40th day). All the rats were sacrificed 8 weeks after the RT administration for histopathological analysis. ***Results*:** Compared with the RT+Surg-10 and RT+Surg-20 groups, the hyalinization and collagenization scores in RT+Surg-30 were determined to be significantly lower. Fibrosis scores were lower in the RT+Surg-30 group compared with the RT+Surg-20 group, whereas significantly lower inflammation scores were determined in the RT + Surg-40 group and significantly higher dermal thickness in the RT+Surg-30 group compared with the RT+Surg-10 group. ***Conclusions*:** The findings from this model of irradiated flap revealed the significance of the time lag among flap application and postoperative RT for histopathological outcome, emphasized the potential role of at least a 30- to 40-day interval between surgery and RT in achieving more favorable flap status.

INTRODUCTION

Breast-sparing surgery pursued by adjuvant radiotherapy (RT) is a mainstay treatment for newly diagnosed, nonmetastatic breast cancer with an established critical role of postmastectomy RT in the reduction of local relapse and improve in the complete survival rates [1-5]. In accordance with improved techniques in reconstructive surgery targeting the restoration of the frame and equality of the mammary tissue rather than simply correcting the postmastectomy chest deformity, transverse rectus abdominis musculocutaneous (TRAM) flap is the flap of choice for autologous breast reconstruction after mastectomy [6, 7]. Several refinements and modifications have led to improved operative techniques since its first description [8, 9]. Although RT is an inbuilt portion of the interdisciplinary modality to breast cancer, the ideal combination with restoration in postmastectomy cases remain a matter of disagreement [10]. Hence, given the ongoing ratio of patient treated with postmastectomy RT, recent interest has focused on the risks in conjunction with RT in autologous tissue flaps [11, 12]. These include early (i.e., vascular thrombosis, flap necrosis, circulatory impairment on the flap, and local wound evolvement) and late (i.e., fibrosis, fat necrosis, loss of flap volume, and contracture of flap) radiation-induced complications, as well as the unforeseen fear to wider cosmetic

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considerations (i.e., loss of breast volume, shape irregularity, asymmetry, and dyspigmentation) complications [13-15]. TRAM flap application is considered a reliable, tolerable, and desirable choice in patients who require adjuvant RT, with suitable rates of complications and favorable aesthetic results having been reported in literature [16-20]. However, careful reconstructive operative planning and timing of RT are considered crucial in minimizing the deleterious effects of adjuvant RT to tissue viability and cosmesis [21, 22].

Nonetheless, alongside the lack of clarity on the ideal time lag among reconstruction and RT, the impact of radiation therapy on flap-based breast reconstruction is often imprecisely defined with the likelihood of early wound healing to have anyway happened in the recipient site, given that RT is not frequently started as well as 1 or 2 months posttransfer of the flap [23]. Although several available rat flap models do not all the time adapt to human anatomy, a TRAM flap is considered to allow broader experimental use as there is notable resemblance between rats and humans. It is both with regards to two blood supplies and the presence of perforator vessels ensuring blood supply for the skin [24, 25]. This study was therefore designed to investigate flap status in relation to the timing of RT in an experimental model of irradiated TRAM flap. Also, the objective of this experimental study was to demonstrate more precisely the postoperative impact of irradiation on TRAM flap. Thus, the findings from this study can assist in reconstructive decision-making on postmastectomy patients.

MATERIALS AND METHODS

Animals

A total of 56 adult, male, 9-month-old, Sprague-Dawley albino rats (250–500 g) were kept in a temperature-, humidity, and light-controlled room with a temperature of 22˚±0.5˚C, relevant humidity of 45.0% ± 10.0%), and 12-h light-dark cycle. The experiments were fed standard rat pellets (TAVAS Inc, Adana, Turkey) and provided with water ad libitum. All experiments were executed in accordance with the protocols confirmed by Dicle University Faculty of Medicine Local Ethics Committee (date of approval: October 27, 2010, protocol no: 2010/38) and complied with the Guide for the Care and Use of Laboratory Animals.

Study protocol

The experiments were separated sub seven groups (n=8 for each) in terms of flap surgery and RT via a computer-generated randomization program. The groups comprised a sham group (no surgery, no RT), control group (Ctrl; surgery without RT), RT-alone group (RT; RT without surgery), and RT plus surgery (RT+Surg) group, which was further separated into four groups depends on the timing of postoperative RT: RT+Surg-10 (RT on postoperative 10th day), RT+Surg-20 (RT on postoperative 20th day), RT+Surg-30 (RT on postoperative 30th day), and RT+Surg-40 (RT on postoperative 40th day) groups. At 8 weeks after the RT administration, all rats were sacrificed using intracardiac blood aspiration. Muscle and cutaneous tissue samples were collected for comparative histopathological analysis of inflammation, fibrosis, focal hyalinization, collagenization, and dermal thickness in seven study groups.

TRAM flap model

The experiments were anaesthetized with 90 mg/kg ketamine (Ketalar® flacon; Pfizer Inc, Istanbul, Turkey) and 10 mg/kg xylazine (Rompun® flacon; Bayer Inc, Munchen, Germany) intramuscularly and were then placed in dorsal decubitus on a smooth surface, fixed with stretched extremities and shaved of the feather on the abdominal surface. The rat TRAM flap model was carried out as defined by Ozgentas *et al.* in 1994 [26]. The superior epigastric artery-based TRAM flap (with 6 × 4-cm Skin Island) was then delineated and raised on ipsilateral superior epigastric artery (figure 1). The muscle flap donor area was closed primarily, and the rectus muscle layer of the TRAM flap was inserted on the donor area. The skin island was turned back to its original position, and the rectus abdominis muscle and skin were sutured to the original position. Then, a closed dressing was applied to the abdominal region without limiting the mobility of the rats. Postoperatively, an oxygen saturation monitoring system (KMA® 800 Patient Monitoring System, PETAŞ, Ankara, Turkey) was placed into the skin island for a short term once daily, and flap survival was monitored (figure 2).

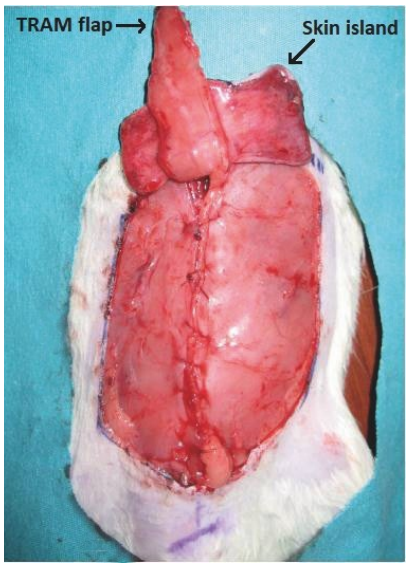

Figure 1. View of the elevation of TRAM flap with skin island.

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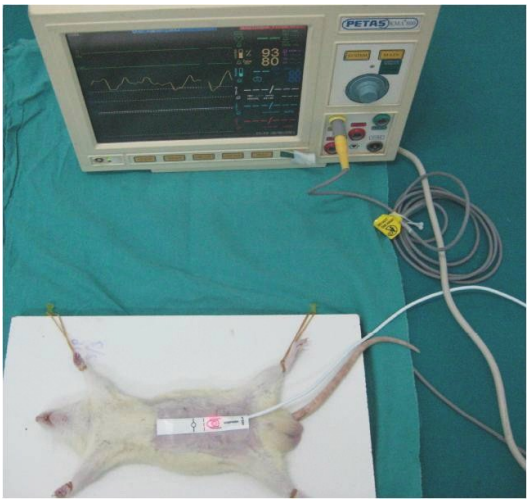

Figure 2. View of the measurements of flap viability by pulse oximeter monitoring.

RT administration

According to the study by Kulahci *et al.* [22], a single 25-Gy-dose external RT was administered to the flap skin island via a 1.25-MV energy cobalt 60 (Co-60, Alcyon-II; GE Medical Systems, Istanbul, Turkey) teletherapy device under ketamine (Ketalar® flacon; Pfizer Inc, Istanbul, Turkey) and xylazine (Rompun® flacon; Bayer Inc, Munchen, Germany) general anesthesia; 0.5-cm bolus doses were gave to cumulate a peak dose onto the flap skin island. Bullet pads enabled to preserve adjacent areas.

Select of radiation dosage

It is reported that the highest alteration in skin surface happens with a single dose of 20-Gy [27-29] and that skin changes are happened after minimum 25-Gy [30]. For these reason, 25-Gy single doses were implemented to the study groups in this experiment.

Histopathology assessment

All components of TRAM flap with 6×4-cm Skin Island were taken for histopathological examination. In this manner, the sample size was standardized, and the study was adequately powered. Desquamation, fibrosis, and ulceration in the skin island were observed macroscopically and epidermal -dermal thickness was measured via light microscope (ECLIPSE 80i; Nikon®, Japan). Tissue samples were fixed in 10% having a buffer formalin and imbedded in paraffin for series of sequencing. Lengthwise 5-µm sections were dyed with hematoxylin and eosin (H&E), and inflammation, fibrosis, collagenization, hyalinization, and necrosis in musculocutaneous tissue were evaluated using a light microscope (ECLIPSE 80i; Nikon®, Japan) (×100 and ×200 augmentation) and scored from 0 to 3 (0/-: no change, 1/+: mild, 2/++: moderate, 3/+++: marked). The observers were blinded to treatment groups of the specimens.

Statistical method

Statistical method was made using IBM SPSS Statistics for Windows, version 24.0 software (IBM Corp®, Armonk, New York, USA). Kruskal-Wallis *H* test and post hoc Dunn test were utilised to analyze differences in histopathological parameters among the study groups. Data are denoted as mean±standard deviation (SD), minimum-maximum, and percentage (%) values where convenient. $P<0.05$ was noted statistically significant.

RESULTS

Both the RT and control groups had similar increase in inflammation scores (P<0.001 and P<0.01, respectively), fibrosis (P<0.001 for each), hyalinization (P<0.01 for each), collagenization (P<0.01 and P<0.001, respectively), and dermal thickness (P<0.001 for each), when compared with the control group (table 1; figure 3).

Inflammation and fibrosis scores were significantly higher than those of the sham group in each RT+Surg group regardless of the timing of RT (*P* values ranged from <0.005 to <0.001). When compared with the sham group values, the RT+Surg-10 and RT+Surg-20 groups had significantly higher median scores for hyalinization (0.0 vs 3.0 [RT + Surg -10] and 2.6 [RT+Surg-20], $P<0.001$ for each) and collagenization (0.0 vs 3.0 [RT+Surg-10] and 2.6 [RT+Surg-20], $P<0.001$ for each) and significantly lower scores for dermal thickness (1.1 vs 0.8 [RT+Surg-10] and 0.9 [RT+Surg-20], $P<0.01$ and P¬4.49, respectively). However, collagenization and dermal thickness scores in the RT+Surg-30 group (1.4 and 1.0, respectively) with hyalinization and dermal thickness scores in the RT+Surg-40 group (1.4 and 0.9, respectively) were normalized with no significant difference from the sham group values (table 1; figures 4-8).

Fibrosis scores were similar in the RT and RT+Surg groups, regardless of the timing of RT. Apart from significantly lower inflammation scores in the RT+Surg-40 group compared with the RT group (1.6 vs 2.6, $P<0.05$), the other RT+Surg groups had similar inflammation scores to the RT group. Apart from significantly higher hyalinization (3.0 vs 2.0, P<0.01) and collagenization (3.0 vs 2.0, P<0.01) scores in the RT+Surg-10 group than in the RT group, other RT+Surg groups had similar hyalinization and collagenization scores to the RT group. Dermal thickness in the RT group (median = 0.6) was significantly lower than that in the RT+Surg-20 (0.9, P<0.01), RT+Surg-30 (1.0, P<0.001), and RT+Surg-40 (0.9, P <0.01) groups, while similar to the RT+Surg-10 (0.8) group (table 1).

Inflammation and fibrosis scores were similar between the control and RT+Surg groups, regardless of the timing of RT. Apart from significantly higher hyalinization scores in the RT+Surg-10 group (3.0 vs 2.0, P<0.01) and lower collagenization scores in the

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RT+Surg-30 group (1.4 vs 2.4, *P*<0.05) than in the control group, no significant difference was considered between the control and RT+Surg groups with regards to hyalinization and collagenization scores. Dermal thickness in the control group (median = 0.7) was significantly lower than in the RT + Surg-30 (1.0, P<0.01) and RT+Surg-40 (0.9, P<0.05) groups, while similar to the RT+Surg-10 (0.8) and RT+Surg-20 (0.9) groups (table 1).

Hyalinization and collagenization scores in the RT + Surg-30 group (1.6 vs 3.0 [RT+Surg-10] and 2.6 [RT+Surg-20], P<0.001 and P<0.05, respectively for hyalinization; 1.4 vs 3.0 [RT+Surg-10] and 2.6 [RT+Surg-20], P<0.001 and P<0.01, respectively for collagenization) and in the RT+Surg-40 group (1.4 vs 3.0 [RT+Surg-10] and 2.6 [RT+Surg-20], P<0.001 and P<0.01, respectively for hyalinization; 1.6 vs 3.0 [RT+Surg-10] and 2.6 [RT+Surg-20], P < 0.01 and P<0.05, respectively, for collagenization) were significantly lower than the scores in the RT+Surg-10 and RT+Surg-20 groups (table 1; figures 6 and 7).

Fibrosis scores were significantly lower in the RT+Surg-30 group compared with the RT+Surg-20 group (1.4 vs 2.0, P<0.05), whereas inflammation scores were significantly lower in the RT+Surg-40 group (1.6 vs 2.6, P<0.05), and dermal thickness was significantly higher in the RT+Surg-30 group (1.0 vs 0.8, P<0.05) compared with the RT+Surg-10 group (table 1; figures 4, 6, 8).

Table 1. Histopathological parameters related to TRAM flap quality in the study groups.

	Inflammation	Fibrosis	Hyalinization	Collagenization	Dermal thickness
Groups	median(min-max)	median(min-max)	median(min-max)	median(min-max)	median(min-max)
Sham (n=8)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	1.1 (0.9-1.7)
RT (n=8)	2.6 (2-3)^{***,q}	1.6 (1-2)***	2.0 (2-2)^{**,ww}	2.0 (2-2)^{**,ww}	0.6 (0.4- 0.8)$^{***,++,ttt,qq}$
Ctrl (n=8)	2.0 (2-2)**	1.6 (1-2)***	2.0 (2-2)^{**,ww}	2.4 (2-3)^{***,t}	0.7 (0.6- 0.9)^{***,tt,q}
RT + Surg-10 (n=8)	2.6 (2-3)***	2.0 (1-3)***	3.0 (3-3)***	3.0 (3-3)***	0.8 (0.6- 0.9)**
RT + Surg-20 (n=8)	2.4 (2-3)***	2.0 (2-2)***	2.6 (2-3)***	2.6 (2-3)***	0.9 (0.8-1)*
RT + Surg-30 (n=8)	2.2 (1-3)***	1.4 (1-2)$^{**,+}$	1.6 (1-2)$^{*,www,+}$	1.4 (1-2)$^{www,++}$	1.0 (0.9-1.5)^{w}
RT + Surg-40 (n=8)	1.6 (1-2)^{*,w}	1.6 (1-2)***	1.4 (1-2)$^{www,++}$	1.6 (1-2)$^{*,ww,+}$	0.9 (0.7- 1)
Total (n=56)	2.1 (0- 3)	1.5 (0-3)	1.9 (0-3)	2.0 (0-3)	0.9 (0.4-1.7)

Flap necrosis was not observed in any of the groups. Ctrl: control; RT: RT alone; RT+Surg: RT plus surgery. *P<0.05, **P<0.01 and ***P<0.001; compared with the sham; wP<0.05, wwP<0.01 and wwwP < 0.001; compared with the RT+Surg-10; +P<0.05 and ++P<0.01; compared with the RT + Surg-20; tP<0.05, ttP<0.01 and tttP<0.001; compared with the RT+Surg-30; qP<0.05 and qqP<0.01; compared with the RT+Surg-40. Kruskal Wallis test (Monte Carlo) and post Hoc Dunn's test.

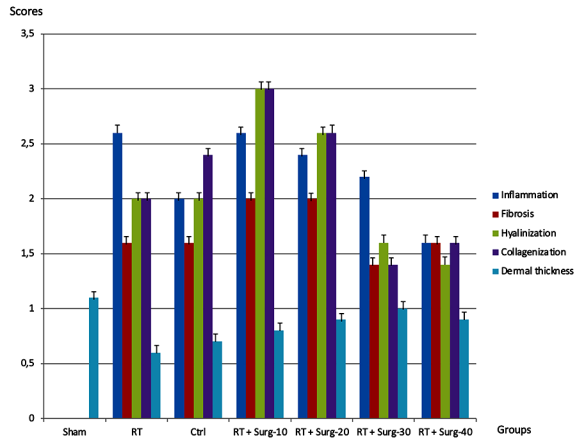

Figure 3. Distribution of histopathological parameters in the study groups.

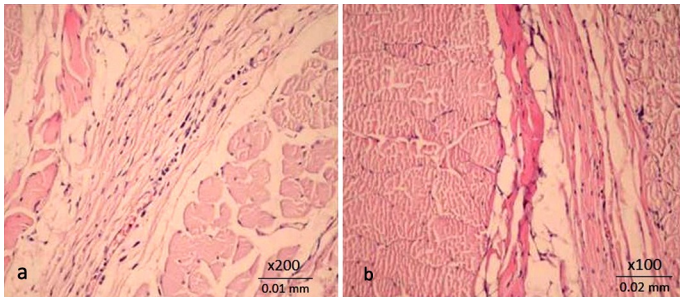

Figure 4. a) Histopathological findings of the degree of inflammation in TRAM flap specimens in RT + Surg-10 group; diffuse inflammation 10-day interval between surgery and RT. **b)** Histopathological findings of the degree of inflammation in TRAM flap specimens in RT + Surg-40 group; mild to moderate inflammation 40-day interval between surgery and RT.

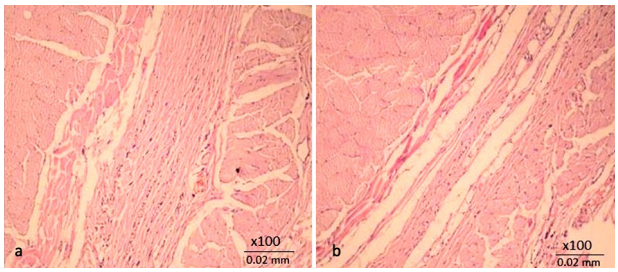

Figure 5. a) Histopathological findings of the degree of fibrosis in TRAM flap specimens in RT + Surg-10 group: diffuse fibrosis 10-day interval between surgery and RT. **b)** Histopathological findings of the degree of fibrosis in TRAM flap specimens in RT + Surg-30 group: mild fibrosis 30-day interval between surgery and RT.

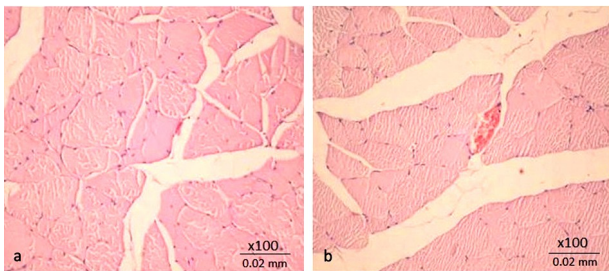

Figure 6. a) Histopathological findings of the degree of hyalinization in TRAM flap specimens in RT + Surg-10 group: diffuse hyalinization 10-day interval between surgery and RT. **b)** Histopathological findings of the degree of hyalinization in TRAM flap specimens in RT + Surg-40 group: mild hyalinization 40-day between surgery and RT.

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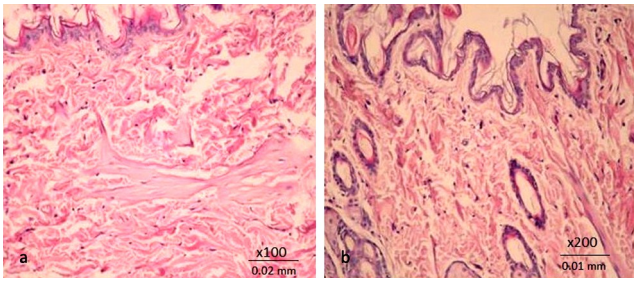

Figure 7. a) Histopathological findings of the degree of collagenization in TRAM flap specimens in RT + Surg-30 group: mild collagenization 30-day interval between surgery and RT. **b)** Histopathological findings of the degree of collagenization in TRAM flap specimens in RT + Surg-10 group: diffuse collagenization 10-day interval between surgery and RT.

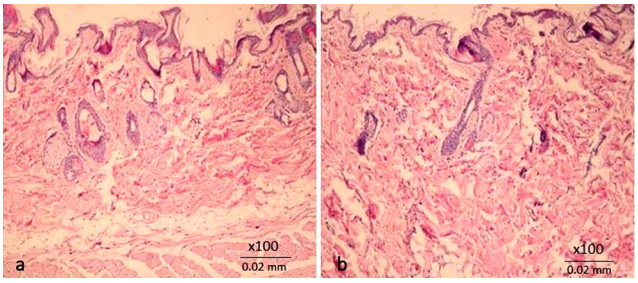

Figure 8. a) Histopathological findings of dermal thickness in TRAM flap specimens in RT group: dermal thinning. **b)** Histopathological findings of dermal thickness in TRAM flap specimens in RT + Surg-40 group: preservation of dermal thickness 40-day interval between surgery and RT.

DISCUSSION

The findings of this study demonstrated more favorable flap outcomes in terms of lower hyalinization and collagenization scores and preservation of dermal thickness with a 30- to 40-day rather than a 10- to 20-day interval between flap surgery and postoperative RT. This finding revealed that at approximately 30 or 40 days were adequately time intervals for prevention of RT induced tissue changes on the flap areas. In addition, fibrosis and inflammation scores at late periods were lower than those at early periods, whereas a 10-day interval was associated with even worse hyalinization and collagenization scores than the RT group. These findings are similar to those of the study by Kulahci et al when the experimental and control groups were compared [22]. However, we think that it provides an additional contribution to the literature on this subject, as our study provides more detailed data.

Although these findings support cutaneous radiation injury with a single-dose 25-Gy irradiation shown in an experimental TRAM flap model in terms of dermal damage and inelasticity, they emphasize the role of the timing of postoperative RT in the extent of irradiation-dependent adverse outcomes. Similarly, in a rat TRAM flap experimental model study, irradiation (50-Gy in 25 fractions; 5 days a week for 5 weeks) of flaps 4 weeks after flap surgery revealed that the flaps were resistant to the adverse effects of irradiation with no significant difference from sham rats in terms of flap thickness, elasticity, dermal scarring, and inflammatory and architectural changes [31, 32].

The importance of the time between surgery and radiation has also been shown in other experimental flap models such as the ventral fasciocutaneous free flap animal model by Angelos *et al.*, which showed an association of lengthier period between vascular clamping and 40-Gy total dose of radiation with substantial increases in flap viability [33]. However, in a study by Yun *et al.*, on the early impressions of postmastectomy radiation on TRAM flap application in breast cancer cases, the interval between surgery and irradiation was not shown to be estimative of an enhanced extent of rash or the ensued of desquamation in the treatment area [34]. However, the advanced studies must be performed to the time frames described and used in these studies, with equivalency between rats and humans.

In addition to the lack of clarity on the ideal time period between breast-preserving surgery and RT [35-39], there is also inconsistency regarding the impact of the time between reconstruction and RT on local relapse and survival with no impact of interval of less than 12 versus more than 12 weeks [40], 0 to 4 weeks versus 8 to 12 weeks [41], and 8 weeks versus 31 weeks [42], whereas poor prognosis has been reported in cases of delaying RT for more than 13 weeks versus 0 to 5 weeks [43], more than 16 weeks versus less than 16 weeks [44], more than 7 weeks versus 7 weeks, and more than 3 months. For these reasons, we believe that approximately 30- to 40-day interval cannot affect cancer recurrence and survival.

Moreover, some authors have suggested delaying reconstruction surgery until RT is complete, given that although neither preoperative nor postoperative irradiation increases the fear for flap or donor-area problems, post-TRAM compared with pre-TRAM radiation has been associated with poor aesthetic outcomes, symmetry, and contracture scores, as well as higher late complication rates and the need for another flap to restore the unshaped contour from flap contraction and severe flap deformation [11]. Nevertheless, most studies have reported a satisfying aesthetic result in cases ongoing TRAM either before (84%-100%) or after RT (66%-88%) [10].

The findings of the current study revealed the potential benefit of delaying irradiation for at least 30 - to 40-day after flap surgery in terms of more favorable histopathological outcomes such as reduced inflammation, fibrosis, hyalinization, and collagenization, as well as the preservation of dermal thickness. Notably, irradiation 10 days after flap surgery was associated with an even poor outcome than the histopathological adverse changes due to RT

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alone.

In addition to the lack of clarity on the optimal time interval between operation and RT, with the diversity of breast reconstruction methods present, selecting the "right" technique mostly proves to be scaring for both surgeons and patients. Research into consequences can ensure surgeons and patients with impartial, safe knowledge to help in reconstructive decision making.

CONCLUSION

These findings revealed the significance of the time lag between flap application and postoperative irradiation. The findings from this study seem to provide a more precise demonstration of the effect of irradiation on flap status, which would assist in reconstructive decision-making.

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***Conflict of Interest*:** None declared.

***Compliance with ethical standards*:** All experiments were performed according to the protocols approved by Dicle University Faculty of Medicine Local Ethics Committee (date of approval: October, 27, 2010, protocol no: 2010/38) and complied with the Guide for the Care and Use of Laboratory Animals.

***Data availability statement*:** The datasets are present over reasonable claim from the corresponding author.

***Author's contribution*:** O.B. wrote the manuscript; P.K.C., M.B. and E.K. revised the manuscript; Y.K., O.S. and C.T.S. did the data analysis; S.B.Z. and O.B. did the data collection.

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