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Original Article

Adipogenesis of bioabsorbable implants under irradiation in a rodent model

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ABSTRACT

Background: Breast cancer is the most common cancer among women. Partial mastectomy is an alternative to mastectomy in early-stage breast cancer to restore a poor quality of life (QOL). However, the aesthetic satisfaction with this procedure is inadequate. The standard methods for breast reconstruction have certain limitations. We developed bioabsorbable implants consisting of an outer mesh composed of poly L-lactic acid (PLLA) and an inner component filled with a collagen sponge (CS). These implants were designed to promote and sustain adipogenesis in vivo, without the addition of exogenous cells or growth factors. In this study, we used PLLA mesh implants to investigate the effects of irradiation on fat formation, which is important in partial mastectomy.

Methods: The implants were inserted into both the inguinal regions of the rats. One month after the implantation, a dose of 13 Gy was delivered to the left-side implants. We compared adipose tissue formation in the non-irradiated and irradiated groups at 6 and 12 months after irradiation.

Results: Irradiation of implants did not lead to malignant tumor formation. The newly formed tissues and adipose tissue were not significantly different between the two groups at 6 and 12 months after irradiation.

Conclusions: PLLA mesh implants containing CS are desirable bioabsorbable implants that can be replaced with autologous adipose tissue after in vivo implantation under irradiation. These implants serve as an effective material for partial mastectomy and have the potential to improve the QOL of patients after mastectomy.

1. Introduction

Breast cancer is the most common cancer among women worldwide [1], and radical surgery is a necessary component of its treatment. Many patients experience a poor quality of life (QOL) after breast cancer surgery due to poor body image and emotional disorders, leading to psychological distress and depression [2–5]. Therefore, improving QOL in patients after surgery has become increasingly important [6,7]. Surgical methods for treating breast cancer have evolved into less invasive techniques. Breast-conserving surgery (BCS), including partial mastectomy, is an alternative to mastectomy for early-stage breast cancer [8,9]. The principal purpose of BCS is to achieve aesthetic satisfaction while preserving oncological radicality [10]. However, BCS cannot always

Abbreviations: QOL, quality of life; BCS, breast-conserving surgery; BIA-ALCL, breast implant-associated anaplastic large cell lymphoma; PLLA, poly-L-lactic acid; CS, collagen sponge; H and E, hematoxylin and eosin; TBST, distilled water and Tris–HCl buffer; BSA, bovine serum albumin; PBS, phosphate-buffered saline.

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satisfactorily achieve both goals [11–13], since the aesthetic outcomes are influenced by lesion/breast ratio and location of the lesion [14].

Currently, breast reconstruction procedures involve the use of autologous flaps, silicone implants, or autologous fat injections. Despite successful outcomes of these procedures, several issues persist, including donor site morbidity and volume loss over time with autologous flaps, development of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) [15], capsule contracture with silicone implants [16], low survival rate, and unproven safety of fat injections [17–19]. Partial mastectomy may result in minimal breast deformity depending on the extent of resection. However, breast reconstruction using autologous flaps or fat grafting is required to achieve aesthetic satisfaction. In addition, patients undergoing partial mastectomy need to be irradiated, highlighting the need for innovative methods that can withstand radiation while restoring breast volume.

Tissue engineering has made progress in regenerating adipose tissue using of cells, growth factors, and scaffolds [20,21]. In vivo, cells and growth factors are supplied by the surrounding tissue. Avoiding in vivo compressive pressure from materials for several months promotes adipose tissue regeneration [22–24]. Therefore, we developed a bioabsorbable implant combining poly-L-lactic acid (PLLA) mesh and collagen sponge (CS) for breast reconstruction after partial mastectomy. This implant serves as a new method in breast reconstruction as it can be replaced with adipose tissue [25,26].

In the present study, we aimed to create an irradiation model using rodents and investigated the effects of irradiation of the implants on fat formation.

2. Materials and methods

2.1. Preparation of implants

As described in the previous study [25], we prepared 26 implants made of PLLA containing CS (CS; PELNAC®, Gunze Ltd., Tokyo, Japan) in the following manner. First, each columnar mesh (10 mm in diameter and 10 mm in height) was knitted with a 2–0 PLLA thread (Gunze Ltd.). The mesh was then densely packed with 40 mm × 20 mm × 3 mm CS with a porosity of 80–95 %. Finally, the top and bottom of the mesh were closed with purse-string sutures using 2-0 PLLA threads. The largest diameter of the short axis was approximately 18 mm, and the equatorial diameter of the sphere was approximately 7.5 mm. On the surface of the implant, the gaps between the meshes were squares measuring approximately 1.5 × 1.5 mm (Fig. 1a).

2.2. Animal experiment

2.2.1. Experimental design and operating procedure

Fourteen male F344/Jcl rats (10–11 weeks old) were purchased from CLEA Japan, Inc. (Osaka, Japan). After a 1-week preservation period, one implant was placed bilaterally in the inguinal region according to the procedure described in a previous study [25]. Rats were anesthetized with 5 % isoflurane (Wako Pure Chemical Industries Ltd, Osaka, Japan) during the induction period and 2.5–3.0 % of isoflurane during the maintenance period. No antibiotics were administered. First, a 2 cm long skin incision was made in the cranial part of the inguinal ligament after shaving and depilating the inguinal region. The inguinal fat pad was incised, a pocket was created, and an implant was placed under the fat pad. The implant was placed in a pocket over the femoral vessels and fixed to the fat pad using 4-0 nylon sutures (Diadem: Wonderworks Inc., Tokyo, Japan). Finally, the fat pad and skin were closed using 4-0 nylon sutures.

2.2.2. Irradiation of implants

One month after implantation, the rats received gamma radiation. First, the rats were anesthetized by intraperitoneal administration of mixed anesthesia comprising 0.375 mg/kg medetomidine hydrochloride (Domitor: NIPPON ZENYAKU KOGYO Co., Ltd., Fukushima, Japan), 2 mg/kg midazolam (Dorumicum: Astellas Pharma Inc., Tokyo, Japan), and 2.5 mg/kg butorphanol tartrate (Bettlefar: Meiji Animal Health Co., Ltd., Kumamoto, Japan). After being fixated onto the cork board, the left limb including the ipsilateral inguinal region of the rats was irradiated using Gammacell® 40 Exactor (Best Theratronics Ltd., Ottawa, Canada). A special shielding device made of low-melting-point lead alloys (Best Theratronics Ltd.) was designed to protect other regions of the rat during radiation exposure (Fig. 2a and b). The implant was designed to be positioned at the center of the irradiated area. According to the linear-quadratic model, the radiation dose was set to 13 Gy, which is comparable to the clinical radiation dose of whole-breast irradiation (50 Gy/25fr.) based on the bioequivalent dose calculations. We also confirmed that 13 Gy radiation was delivered

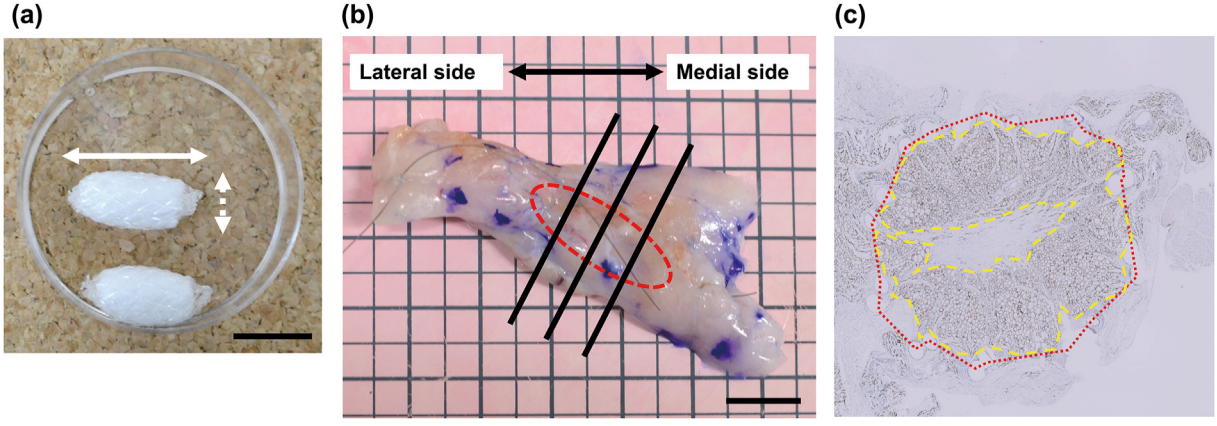

Fig. 1. (a) Gross appearance of the implants. The implant consisted of a poly L-lactic acid mesh with a collagen sponge. The dashed white arrow indicates the greatest diameter of the short axis of the implant, and the solid white arrow indicates the greatest length of the long axis of the implant. Scale bar = 1 cm. (b) Histological assessment of the newly formed tissue in the inguinal region. The area enclosed by the red dotted line represents the shape of the implant. The implant is divided into four equal parts along the long axis, as indicated by the straight black line. Scale bar = 1 cm. (c) Evaluation of the area of newly formed adipose tissue inside implants. The red dotted line shows the area of newly formed tissue, and the yellow dotted line shows the area of newly formed adipose tissue inside the implants.

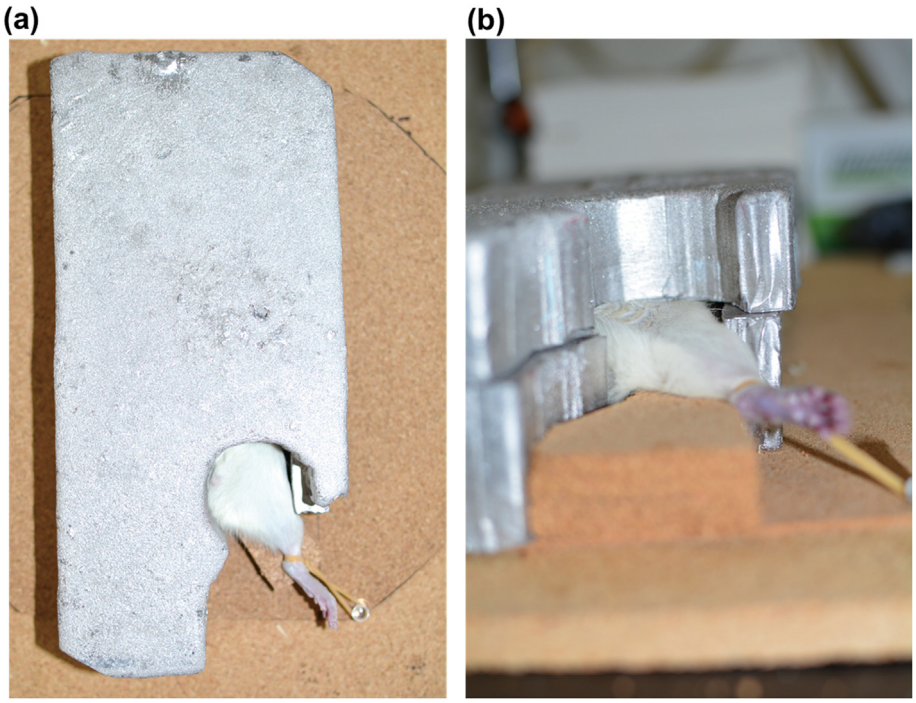

Fig. 2. The lead shield under irradiation. (a) Front view; (b) caudal views.

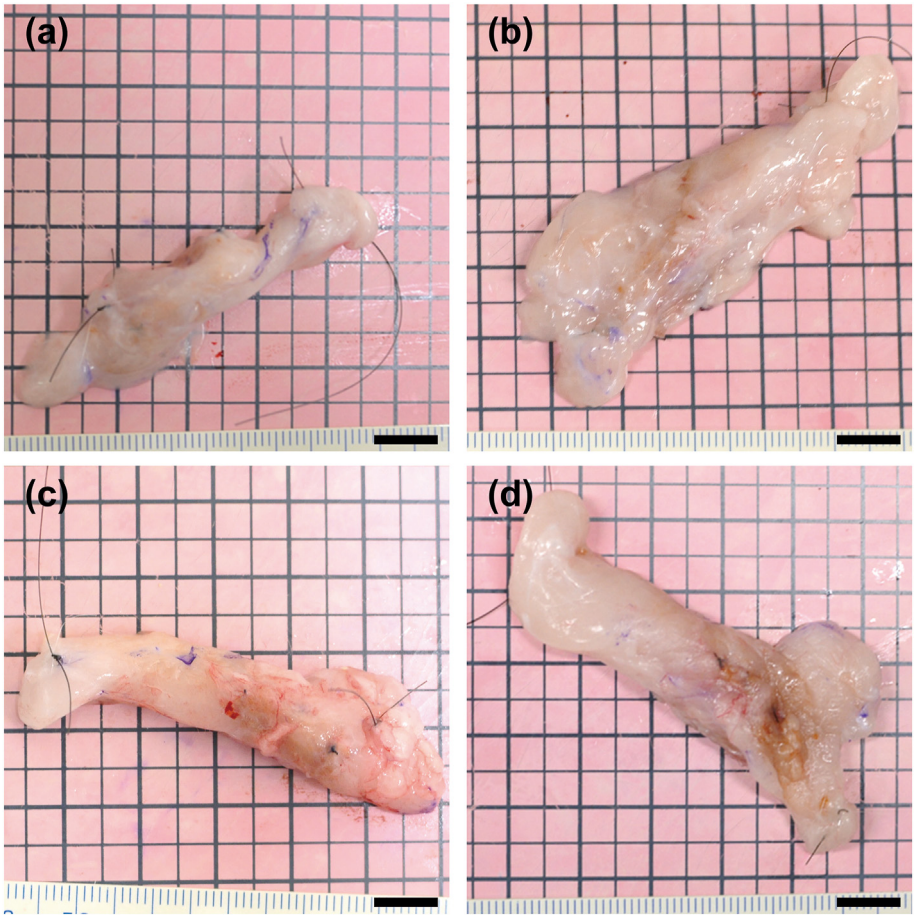

Fig. 3. Gross appearance of all newly formed tissues. The gross appearance of the irradiated group at (a) 6 and (b) 12 months after irradiation. The gross appearance of the non-radiated group at (c) 6 and (d) 12 months after irradiation. Scale bar = 1 cm.

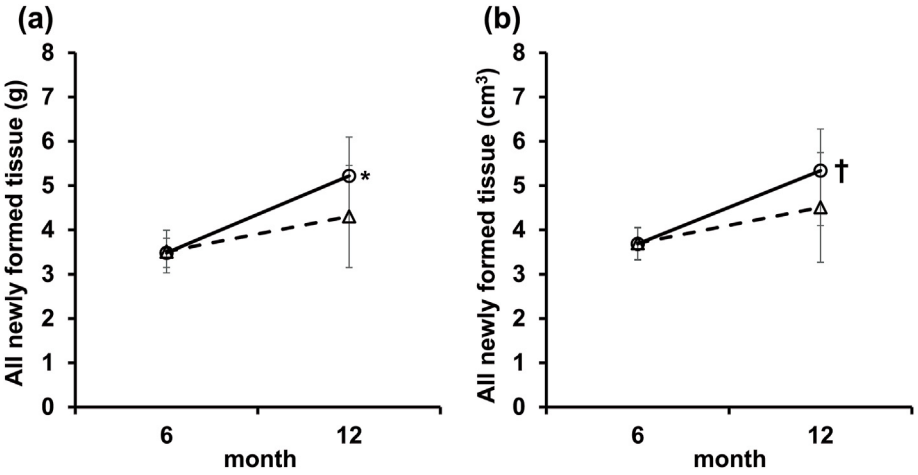

Fig. 4. Weight and volume of all newly formed tissues. (a) Time course of the weight of all newly formed tissues. (b) Time course of the volume of all newly formed tissues. No significant difference was observed between the two groups at 6 or 12 months after irradiation. Data are presented as mean ± standard deviation. *$p < 0.01$ versus at the 6 months, †$p < 0.01$ versus at the 6 months. ○ = non-irradiated group;, △ = irradiated group.

to the central part of the implants using a radiochromic film (GAFCHROMIC EBT-3; VERITAS Corporation, Tokyo, Japan). After irradiation, 0.75 mg/kg atipamezole hydrochloride (Antisedan: NIPPON ZENYAKU KOGYO Co., Ltd.), an anesthetic antagonist of midazolam, was administered via intraperitoneal injection.

2.2.3. Evaluation of the weight and volume of all newly formed tissues

Three rats were euthanized by carbon dioxide inhalation at 6 and 12 months after irradiation. All newly formed tissues were harvested from the iliac crest, the midline area above the muscle

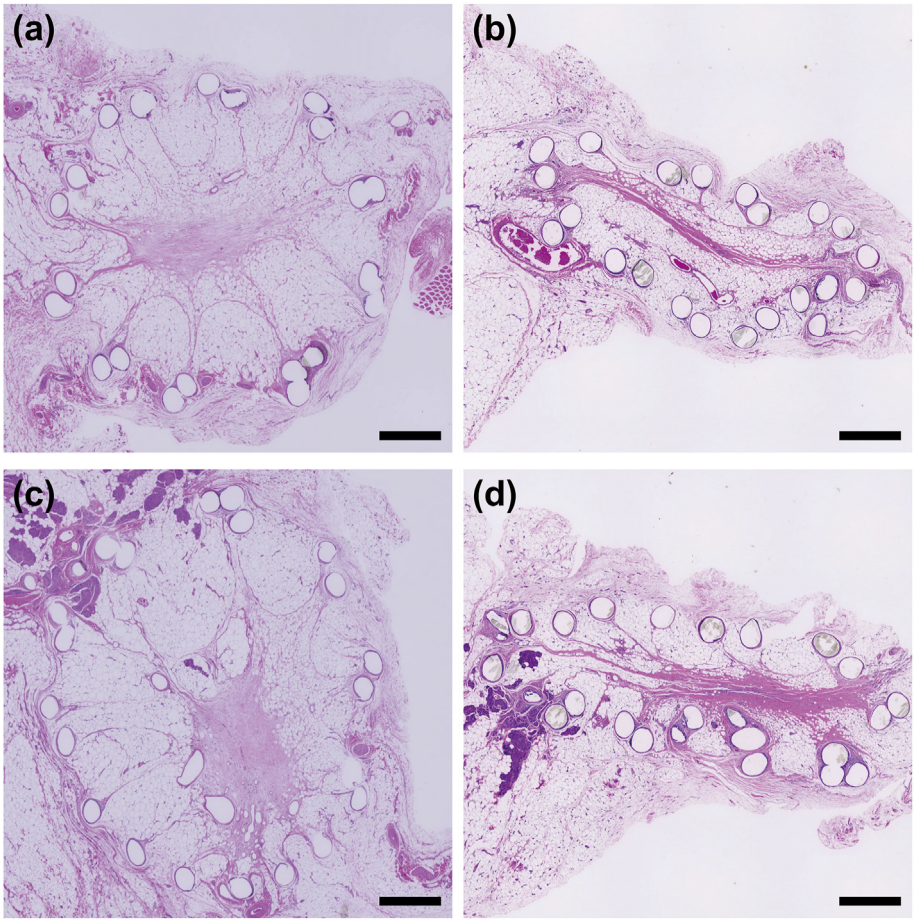

Fig. 5. Light micrographs of the hematoxylin- and eosin-stained sections of the newly formed tissue. Light micrographs of the irradiated group at (a) 6 and (b) 12 months after irradiation. Light micrographs of the non-radiated group at (c) 6 and (d) 12 months after irradiation. The PLLA threads were confirmed up to 12 months after irradiation. Scale bar = 1 mm.

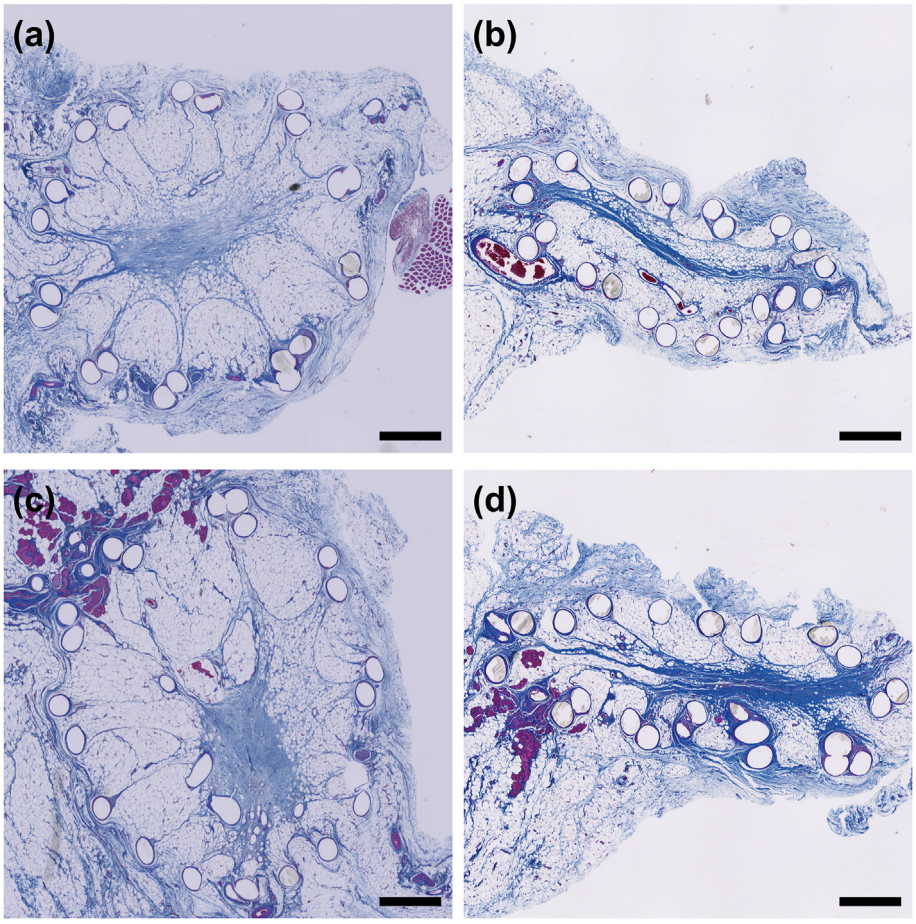

Fig. 6. Light micrographs of the Azan-stained sections of the newly formed tissues. Light micrographs of the irradiated group at (a) 6 and (b) 12 months after irradiation. Light micrographs of the non-radiated group at (c) 6 and (d) 12 months after irradiation. Collagen formation was confirmed at the center of the implants at 12 months after irradiation in both the groups. Scale bar = 1 mm.

layer in the abdominal region, and the area above the muscle layer in the femoral region. The weight of each harvested specimen was measured using an electronic balance (PM460; Mettler-Toledo International Inc., Tokyo, Japan), and the volume was determined using a common water displacement approach [27].

2.2.4. Histological assessment of the newly formed tissue inside the implants

Harvested specimens were fixed in a 10 % formalin neutral buffer solution (FUJIFILM Wako Pure Chemical Industries, Corporation, Osaka, Japan). Each specimen was equally divided into four pieces along the long axis, resulting in three cross-sections (Fig. 1b). The blocks were embedded in paraffin and stained with hematoxylin and eosin (HE), Azan, and immunohistochemical stains. Subsequently, 3-μm-thick HE-stained sections were prepared at the respective three aspects. A 3-μm-thick Azan-stained section was prepared at the central aspect. All images were captured with a Keyence BZ-X800 microscope (KEYENCE Corp., Osaka, Japan) at ×40 magnification.

2.2.5. Evaluation of immunohistochemical staining

Immunohistochemical staining for perilipin was performed to evaluate the newly formed adipose tissue inside the implants. The 3-μm-thick paraffin sections were deparaffinized and dehydrated, followed by immersion in antigen inactivation solution (code: 415211; Nichirei Biosciences Inc., Tokyo, Japan) for 20 min at 98 °C in a water bath. After cooling to room temperature, the sections were rinsed with distilled water and immersed in 3 % hydrogen peroxide for 10 min at room temperature. The sections were then rinsed twice for 5 min in distilled water and Tris–HCl buffer (containing 0.05 % Tween-20 and 0.15 M NaCl) (TBST). To block nonspecific protein binding, sections were immersed in 3 % bovine serum albumin (BSA) diluted in phosphate-buffered saline (PBS) for 60 min at room temperature. Rabbit monoclonal antibody (Perilipin-1 [D1D8] XP® Rabbit mAb #9349S; Cell Signaling Technology, Danvers, Massachusetts) at a 1:200 dilution was applied to the sections and incubated overnight at 4 °C. The sections were rinsed in TBST three times for 5 min each. Thereafter, the sections were stained with rabbit anti-goat simple stain MAX-PO (Histofine 724142; Nichirei Biosciences Inc., Tokyo, Japan) at room temperature for 30 min. The sections were rinsed again with TBST, exposed to DAB (3-3′-diaminobenzidine-4HCl) (Signal Stain® DAB Substrate Kit 725191; Nichirei Biosciences Inc., Tokyo, Japan), and counterstained with hematoxylin. All images were captured with a Keyence BZ-X800 microscope (KEYENCE Corp.) at ×40 magnification. The areas of the newly formed tissue and adipose tissue inside the implants were manually measured using the BZ-X800 Analyzer software (Keyence Corp.) (Fig. 1c). The average area of the three cross-sections of each specimen was used for statistical analysis of the newly formed tissue and adipose tissue inside each implant.

Immunohistochemical staining with anti CD31 antibody was performed to evaluate angiogenesis inside the implants. After

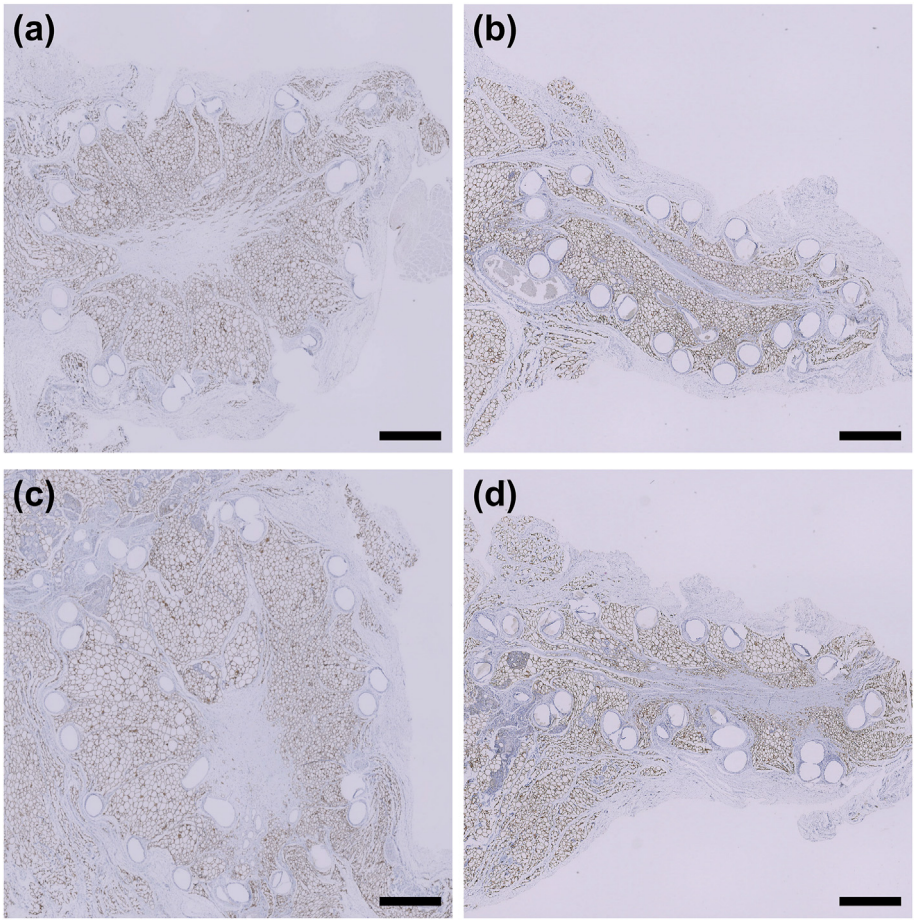

Fig. 7. Light micrographs of the perilipin-stained sections of the newly formed tissue. Light micrographs of the irradiated group at (a) 6 and (b) 12 months after irradiation. Light micrographs of the non-radiated group at (c) 6 and (d) 12 months after irradiation. Adipose tissue expanded from the perimeter of the implant after irradiation. Scale bar = 1 mm.

deparaffinization and dehydration, 3-μm-thick paraffin sections were immersed in an antigen inactivation solution, incubated at room temperature, rinsed in distilled water, immersed in 3 % hydrogen peroxide, rinsed in distilled water, and immersed in TBST, as described above. Nonspecific protein binding was blocked with BSA in PBS. Sections were incubated with primary antibody (Anti-CD31 [EPR17259] Rabbit Monoclonal Antibody ab182981; Abcam plc, Cambridge, UK), overnight at 4 °C. Primary antibodies were diluted at 1:10,000 in 1 % BSA in PBS. Sections were then rinsed in TBST, treated with peroxidase-labeled secondary antibody at room temperature, rinsed in TBST, exposed to 3-3' diaminobenzidine, and counterstained with hematoxylin, as described above. All images were captured with a Keyence BZ-X800 microscope (KEYENCE Corp.) at ×40 magnification.

2.3. Statistical analysis

Differences between samples were examined to determine statistical significance using analysis of variance and the Student's t-test. All data are expressed as mean ± standard deviation, and statistical significance we determined at p values < 0.05. All statistical analyses were conducted using Microsoft Excel with Statcel3 software add-in (Oms Publishing Inc., Tokyo, Japan).

3. Results

During the follow-up period, no infection, hematoma, ulcer formation, or contracture was observed at the irradiated site. The malignant tumor formation around the implants was not observed, and one rat with benign tumors, sebaceoma on the lower abdomen and epidermal cyst on the left thigh, was excluded from the study.

3.1. Evaluation of weight and volume of all newly formed tissues

Representative images of all newly formed tissues at 6 and 12 months after irradiation are illustrated in Fig. 3. All newly formed tissues increased in size over time. The PLLA threads were macroscopically visible for up to 12 months after irradiation. The time courses of the weight and volume of all newly formed tissues are shown in Fig. 4a and b, respectively. The weight and volume of all newly formed tissues in the non-irradiated group at 12 months were significantly greater than those at 6 months. No significant difference was observed between the two groups at 6 and 12 months after irradiation.

3.2. Histological assessment of the newly formed tissue and adipose tissue inside implants

Micrographs of the hematoxylin- and eosin-stained sections of the newly formed tissues are shown in Fig. 5. The PLLA threads were visible for up to 12 months after irradiation. The internal space of the implants was maintained for up to 6 months after irradiation, but they gradually flattened by 12 months after irradiation. Micrographs of the Azan-stained sections of the newly formed tissues are shown in Fig. 6. Collagen formation was confirmed at the center of the implants at 12 months after

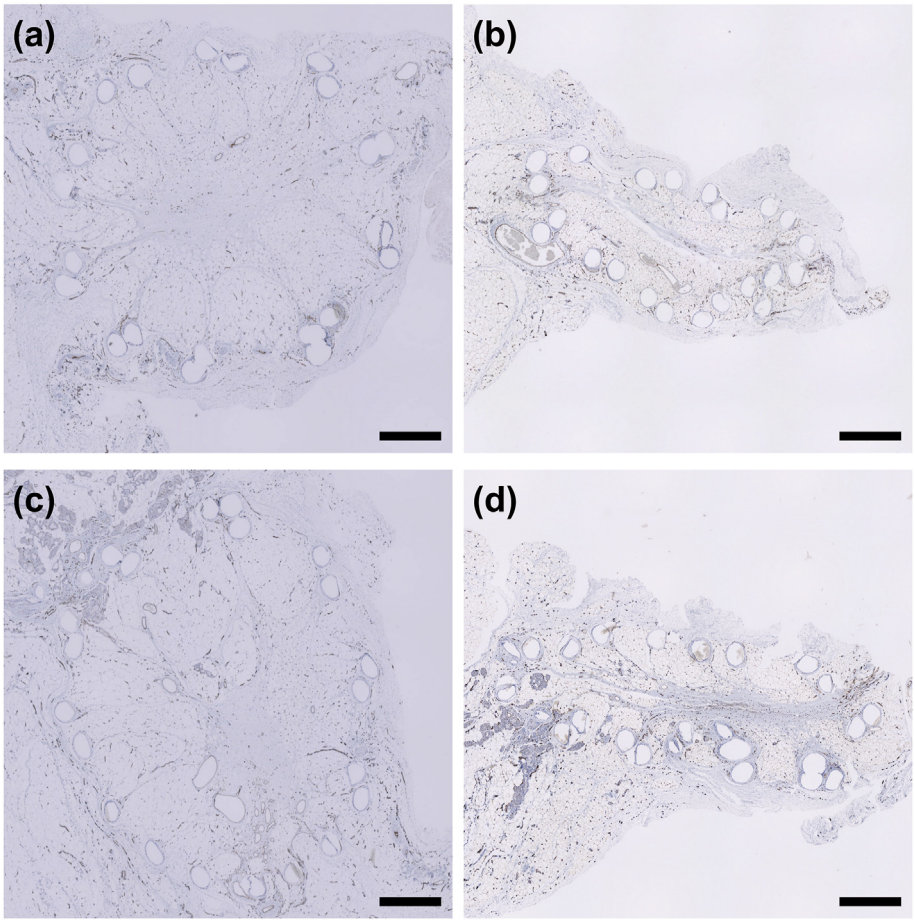

Fig. 8. Light micrographs of the CD31-stained sections of the newly formed tissues. Light micrographs of the irradiated group at (a) 6 and (b) 12 months after irradiation. Light micrographs of the non-radiated group at (c) 6 and (d) 12 months after irradiation. The formation of blood vessels inside the implants was similar in both the groups. Scale bar = 1 mm.

irradiation in both the irradiated and non-irradiated groups. Micrographs of the perilipin-stained sections of the newly formed tissues are shown in Fig. 7. The adipose tissue expanded from the perimeter of the implant in contact with the native adipose tissue after implantation. Micrographs of the CD31-stained sections of the newly formed tissues are shown in Fig. 8. Many blood vessels were identified in the adipose and non-adipose tissue areas inside the implant in both the irradiated and non-irradiated groups.

3.3. Evaluation of the area of newly formed tissue and adipose tissue inside implants

The area of newly formed tissue inside the implants is shown in Fig. 9a. The area of newly formed tissue inside the implant in both the irradiated and non-irradiated groups was significantly smaller at 12 months after irradiation than at 6 months. The area of newly formed adipose tissue inside the implants is shown in Fig. 9b. The

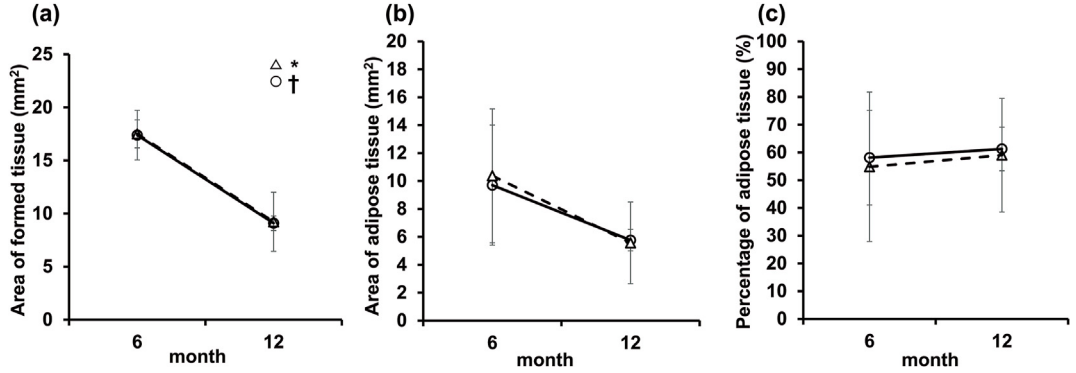

Fig. 9. Evaluation of the area of newly formed and adipose tissues, as well as the percentage of adipose tissue inside the implants. (a) The area of newly formed tissue inside the implant. (b) The area of newly formed adipose tissue inside the implant. (c) Percentage of adipose tissue in the newly formed tissue inside the implant. No significant differences were observed between the irradiated and non-irradiated groups in the areas of newly formed and adipose tissue and the percentage of adipose tissue at any point. Data are presented as mean ± standard deviation. *$p < 0.05$ versus at 6 months, †$p < 0.01$ versus at 6 months. ○ = non-irradiated group;, △ = irradiated group.

area of newly formed adipose tissue inside the implant was not significantly different between 6 and 12 months in either group. The percentage of adipose tissue in the newly formed tissue inside the implants is shown in Fig. 9c. The percentages did not differ significantly between 6 and 12 months in either group. No significant differences were observed between the irradiated and non-irradiated groups in the areas of newly formed and adipose tissue and the percentage of adipose tissue at any point.

4. Discussion

In this study, the adipogenesis of our implants, consisting of a PLLA mesh with CS, was evaluated in rodents exposed to radiation, with a focus on its potential applications for patients after partial mastectomy. Our implants were able to regenerate adipose tissue even after being exposed to radiation, and no malignant tumor formation occurred.

The effects of local irradiation on the skin include redness and dermatitis in the early stage, and pigmentation, dry skin, fibrosis, and ulcer formation in the late stage. Radiation-induced secondary cancers have also been reported [28]. After partial mastectomy, there is a risk of developing soft tissue sarcoma after irradiation [29–31]. In this study, irradiation neither inhibit the increase in the weight and volume of all newly formed tissues nor did it promote the formation of malignant tumors on the skin or implants in Figs. 3 and 5. Therefore, our PLLA implants can be a safe material to be used in breast reconstruction with irradiation.

The formation of adipose tissue, especially in the area of the implant in contact with the native adipose tissue, was confirmed in both the irradiated and non-irradiated groups at 6 months after irradiation in Fig. 7. In addition, collagen fiber formation and angiogenesis inside the implants were similar between the two groups in Figs. 6 and 8. In our previous reports in a rodent model without irradiation, adipose tissue was not regenerated at 1 month after implantation in Supplementary file [32] and was regenerated inside implants at 6 months after implantation [25]. The mechanism of adipogenesis using our implant is as follows: angiogenesis occurs inside implants within the first 3 months after implantation, and adipose tissue differentiates at 6 months after implantation [32]. Contact with the native adipose tissue is a key factor for adipose tissue regeneration [33]. Subcutaneous adipose tissue is highly sensitive to irradiation, leading to decreased proliferation and differentiation capacities [34]. The irradiation in this study did not inhibit adipogenesis and angiogenesis inside the implant. These results indicate that the adipogenesis mechanism using our implants under irradiation is presumed to be the same as in the previous study. Our implants can also regenerate adipose tissue under irradiation and can be used as an adipose tissue-regenerative material after partial mastectomy.

The maintenance of the internal space using bioresorbable materials in combination with fat injection [35], growth factors [36], or cells [22,37] leads to the regeneration of adipose tissue in vivo. A large amount of adipose tissue regeneration using bioabsorbable materials using polycaprolactone-based scaffolds in a porcine model [35] or poly-4-hydroxybutyrate mesh scaffolds in a clinical trial [38] combined with autologous fat transfer has been reported. Our implants, composed of PLLA threads that are absorbed within a few years, avoid complications caused by non-absorbable materials, and are less likely to induce BIA-ALCL. In addition, our implants can regenerate the adipose tissue without the addition of growth factors or cells having the potential to promote recurrence and metastasis; thus, they can be considered as a novel and safe material for breast reconstruction after mastectomy. Moreover, our implants can be made into bioresorbable aggregates that can be reshaped [33] and used to fit tissue defects during surgery. Consequently, our implants can meet the aesthetic demands of patients with breast cancer after partial mastectomy, leading to improved QOL.

This study has several limitations. First, the observation period was limited to 1 year. Therefore, the investigation of long-term observations after irradiation is insufficient. In future studies, we intend to observe the effects of irradiation using a minipig model over a long term. Second, the amount of regenerated adipose tissue was low, and the retention rate of the regenerated adipose tissue was low at 12 months after irradiation. In addition, the regenerated adipose tissue did not lead to an increase in total adipose tissue volume due to the growth of the inguinal adipose tissue in the rats and the low amount of regenerated adipose tissue. Therefore, we need to redesign the shape and material of the implant and conduct an investigation using a minipig model.

5. Conclusion

Our implants regenerated the adipose tissue after irradiation. Our implants may be safe and convenient for breast reconstruction after partial mastectomy.

Author contributions

S. L. and N. M. designed the study. Y. K. prepared the materials, and M. I. prepared the radiation shield. S. L., T. N., Y. K., and M. S. performed the experiments. S. L., S. O., M. S., T. M., T. Y., and N. M. analyzed the data. S. L., S. O., and N. M. wrote and revised the manuscript. N. M. was the grant recipient.

Ethics statement

The animals were maintained at the Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University, Japan. The experimental protocol was approved by the university's Animal Research Committee (Permit Number: Med Kyo19124). A small number of animals was used for this study, and all efforts were made to reduce animal suffering in accordance with the protocols established by the Animal Research Committee of Kyoto University.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2024.10.002.

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