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Adipose-derived regenerative cells and fat grafting for treating breast cancer-related lymphedema: Lymphoscintigraphic evaluation with 1 year of follow-up

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Summary *Background:* Breast cancer-related lymphedema (BCRL) is a feared late complication. Treatment options are lacking at present. Recent studies have suggested that mesenchymal stromal cells can alleviate lymphedema. Herein, we report the results from the first human pilot study with adipose-derived regenerative cells (ADRCs) for treating BCRL with 1 year of follow-up.
Material and methods: We included 10 patients with BCRL. ADRCs were injected directly into the axillary region together with a scar-releasing fat grafting procedure. Primary endpoint was change in arm volume. Secondary endpoints were change in patient-reported outcomes, changes in lymph flow, and safety.
Results: During follow-up, no significant change in volume was noted. Patient-reported outcomes improved significantly with time. Five patients reduced their use of conservative management. Quantitative lymphoscintigraphy did not improve on the lymphedema-affected arms. ADRCs were well tolerated, and only minor transient adverse events related to liposuction were noted.

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Conclusions: In this pilot study, a single injection of ADRCs improved lymphedema based on patient-reported outcome measures, and there were no serious adverse events during the follow-up period. Lymphoscintigraphic evaluation showed no improvement after ADRC treatment. There was no change in excess arm volume. Results of this trial need to be confirmed in randomized clinical trials.

Introduction (Evidence rating scale for therapeutic studies: Level IV)

Breast cancer-related lymphedema (BCRL) is one of the most common and serious late complications following breast cancer surgery with axillary lymph node involvement as up to one-third of patients develop BCRL [1]. Although several microsurgical techniques have been presented during the past decades, they continue to be somewhat experimental owing to the lack of clear evidence; therefore, conservative management remains the standard of care. Preclinical and sparse clinical studies have suggested that cell therapy using autologous mesenchymal stromal cells from various sources including the adipose tissue, muscle, and bone marrow can alleviate lymphedema [2]. The two studies performed thus far in humans have been conducted with cells derived from the bone marrow [3,4].

We were the first to demonstrate the initial 6 months feasibility and safety of transplanting adipose-derived regenerative cells (ADRCs) combined with fat grafting in 10 patients with BCRL (NCT02592213/) [5]. Herein, we report the outcomes after 12 months, which now include follow-up quantitative lymphoscintigraphy results evaluating the lymph drainage following ADRC treatment.

Material and methods

Study design and eligibility criteria

We conducted a prospective, open-label, single-arm, and single-center feasibility and safety study evaluating ADRC injection and fat grafting for the treatment of BCRL. Initially, we screened 34 potential participants and enrolled 11 patients. One patient was subsequently excluded owing to nonprotocolled treatment; hence, results from 10 patients are reported in this study. Inclusion of patients began in November 2015, with the treatments provided between January 2016 and May 2016.

The eligibility criteria for participation were as follows: age between 18 and 70 years, unilateral BCRL, International Society of Lymphology (ISL) stage I or II [6], recurrence-free disease for minimum 1 year, circumference difference of either upper or lower arm of 2 cm between the healthy and the lymphedema arm, American Society of Anesthesiologists physical status score 1 or 2, written informed consent, and the ability to understand the Danish language. The exclusion criteria were as follows: history of other cancer types, diabetes mellitus, psychiatric conditions that could interfere with participation, and tobacco use, which was not ceased in relation to the procedure.

Approvals

The study was approved by The Regional Committees on Health Research Ethics for Southern Denmark (S-20,150,109). The study was also registered with the Danish Data Protection Agency (2008-58-0035) and registered at Clinicaltrials.gov before inclusion of the first patient (NCT02592213). All patients provided written informed consent before participation. ADRC preparation was carried out in an authorized tissue establishment (Danish Health and Medicines Authority, Authorization no. 29,035) for the handling of human tissues and cells at Odense University Hospital, Denmark.

The experimental procedure

All procedures have previously been described in detail [5]. Briefly, liposuction was performed under general anesthesia without administering local anesthetics, as the effect of these on ADRC viability is uncertain [7]. We aimed to obtain 300 mL of lipoaspirate for ADRC isolation and 30 mL of lipoaspirate for fat grafting. ADRC isolation was performed using an automated processing Celution® 800/CRS system (Cytori Therapeutics, San Diego, California, USA) according to the manufacturer's instructions. The final cell suspension was transferred into a 5 mL syringe, of which 1 mL was used for cell characterization and 4 mL for transplantation.

The lipoaspirate for grafting was decanted for 15 min and injected in a fan-shaped pattern into the axilla using a sharp cannula to release the scar tissue. No further scar-releasing measures were undertaken. The isolated ADRCs were injected at eight predefined points in the axilla adjacent to the axillary scar, in the same area where fat grafting was performed. At each point, 0.5 mL of the suspension was injected using a 25 gauge cannula up to a total of 4 mL. The treatment was given as a same-day procedure.

Cell characterization

Total viable nucleated cell recovery and viability percentage were determined using the NucleoCounter NC-100 (ChemoMetec, Allerod, Denmark). Cellular components were identified by flow cytometry analysis with a panel of cell surface markers (CD34, CD90, CD31, CD73, CD235a-CD45-CD31-CD34+, and CD235a-CD45-CD31+CD34+) in

agreement with International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT) recommendations [8].

Endpoints

Patients were evaluated at 1, 3, 6, and 12 months after ADRC injection and fat grafting. The primary endpoint was change in arm volume. Secondary endpoints were change in patient-reported outcomes, change in lymph drainage, and safety evaluation.

Volume estimation

The volume of each arm was calculated by two methods: multiple circumference measurements (1, 3, 6, and 12 months) and dual-energy X-ray absorptiometry (DXA) (3, 6, and 12 months). The excess arm volume was defined as the volume difference between the two arms for both methods. As previously described [9], circumference measurements were made at five points on each arm: wrist, largest point on the lower arm, elbow, middle of upper arm, and proximal on the upper arm. The length between each point was measured, and at each time point, the same sites were used. On the basis of these five measurements, the arm was divided into four segments, and the volume of each segment was calculated using the truncated cone formula:

$$V = \frac{h(C_1^2 + C_1C_2 + C_2^2)}{12\pi}$$

where V is the segment volume, h is the length of the segment, and C_1 and C_2 are the two circumference measurements at the two ends of the segment. Arm volume was calculated as the sum of the four segmental volumes.

DXA was performed as two whole-body scans, with the patient lying in a modified supine position enabling the arm to be separated from the trunk. For analysis, a blinded assessor drew the region around the arm with the proximal end of the arm defined as a region just below the deltoid muscle. As previously described, bone mineral content, fat mass, and lean mass were used to calculate a total arm volume based on known densities [10].

Patient-reported outcomes

All patient-reported outcomes were evaluated at 1, 3, 6, and 12 months. Patients were asked to rate the feeling of heaviness and tension in the lymphedema arm on a numerical rating scale ranging from 0 to 10, with 0 indicating no heaviness/tension at all and 10 signifying the worst heaviness/tension imaginable [11]. Additionally, two questionnaires were used: the Disabilities of the Arm, Shoulder and Hand (DASH) outcome questionnaire [12] and the Lymphedema Quality-of-Life Questionnaire (LYMQOL) [13].

Lymphoscintigraphy

Lymphoscintigraphy was performed according to a procedure described in detail elsewhere [14,15]. The procedure was performed before treatment and after 12 months.

In brief, we injected 0.1 mL of 20 MBq technetium-99m-labeled human serum albumin (Tc-99m-HSA [Vasculocis, CIS Bio International, Paris, France]) into the finger web between the second and third fingers bilaterally. We obtained sequential 5-minute scans every 30–45 min for 5 h. After drainage from the injection site into the collecting lymphatic vessels, the Tc-99m-HSA tracer mimics the lymph fluid flow through the arm. The mean transit time (MTT) of the tracer was calculated for each arm as previously described [14]. MTT is a quantitative measure of the time at which the lymph fluid traverses the arm. We compared the baseline and postoperative MTT.

Statistical analyses

Continuous data were represented as mean ± SD (standard deviation), and nonparametric data were represented as median (interquartile range (IQR)). Patient-reported outcomes were analyzed with the Friedman's test for multiple nonparametric comparisons and with Dunn's post-hoc test for multiple comparisons. Volumetric changes were analyzed by one-way analysis of variance (ANOVA) with Dunnett's post-hoc test for multiple comparisons. Agreement between the two volumetric measurements was tested by generating a Bland-Altman plot. MTT was analyzed with paired or unpaired *t*-test. Two-way ANOVA was performed with the Tukey's test for multiple comparisons for subgroup analysis. A two-tailed *p*-value of less than 0.05 was considered as statistically significant. Statistical analyses were performed using Prism 6 (GraphPad Software, La Jolla, CA, USA).

Results

Ten patients (median age 55 years, range 34–68 years) had unilateral BCRL with a median duration of 28.5 months (IQR 17.3 months) and were in a stable phase of their conservative management; see Supplemental Table 1 for baseline data. For ADRC treatment, 252 g ± 42 g of the adipose tissue was harvested for cell isolation, from either the abdomen or the thighs depending on availability and preference of the patient. Preliminary 6 month results have previously been published [5]. ADRC isolation and characterization using the automated Celution® system were comparable to previous results [16] (Supplemental Table 2). We injected $5.41 \times 10^7 \pm 0.97 \times 10^7$ CERCs and 28.1 mL ± 7.8 mL lipoaspirate into the axillary region to release the scar tissue. The viability of the cells was 83.4, 3.0% (mean, SD), and 24.9, 8.0% (mean, SD) of the cells were defined as stromal stem cells based on surface markers CD45-CD34 + CD31-.

We measured the change in excess arm volume with time by two different methods (DXA and multiple circumference measurements). Although differences in absolute volume were present between the results obtained from the two methods, there was acceptable agreement between

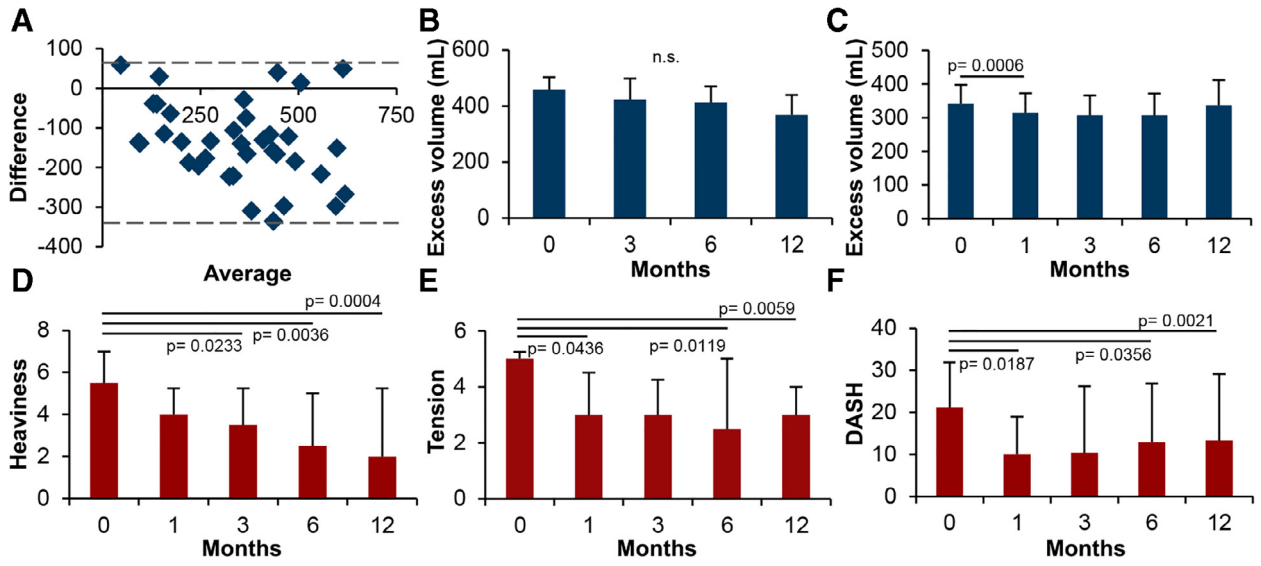

Figure 1 Change in excess arm volume and patient-reported outcomes.
(A) There was good agreement between volume measurements obtained by multiple circumference measurements and DXA, although DXA scan trended toward estimating a greater volume difference between arms. Dashed lines symbolize 95% confidence interval. (B) There was no significant change in excess arm volume measured by DXA (results shown as mean ± SEM). (C) There was only a slight decrease in excess arm volume after 1 month calculated by multiple circumference measurements, but this decrease did not persist and excess arm volume was nearly identical to baseline after 12 months (results shown as mean ± SEM). There was a clear reduction in patient-reported outcomes with regard to heaviness (D), tension (E), and the DASH questionnaire (F) (results shown as median (IQR)).

the two measurements (Figure 1A). There was no significant decrease in arm volume as estimated by either of the two methods for the 12 month period (Figure 1B and C). Subgroup analyses based on ISL stage revealed a tendency toward better volumetric outcomes evaluated by DXA for stage I patients compared with stage II patients ($p = 0.0858$) (Supplemental Figure 1).

In general, the patients reported a decrease in their lymphedema symptoms with time. The median (IQR, $n = 10$) score for heaviness of the arm was 5.5 (4.0) at baseline, 2.5 (4.3) after 6 months, and 2.0 (4.5) after 12 months ($p < 0.0001$) (Figure 1D). Similarly, we found the median score for arm tension to be 5.0 (1.5) at baseline, 2.5 (4.3) after 6 months, and 2.0 (3.0) ($p = 0.0054$) after 12 months (Figure 1E). The DASH questionnaire was also used, wherein the median score was 21.3 (23.5) at baseline, 12.9 (26.0) after 6 months, and 13.3 (28.5) after 12 months ($p = 0.0061$) (Figure 1F). Finally, the LYMQOL questionnaire showed a significant improvement in the symptom subscale after 12 months ($p = 0.0150$). The other subscales failed to meet a significance level at 12 months of follow-up. For an overview of all results, see Supplemental Table 3.

Moreover, five patients reduced their use of conservative treatment in the follow-up period (one discontinued entire therapy, one reduced the size of compression garment, one reduced the use of compression garment, and two no longer needed to wear a compression garment on the hand). Four patients experienced problems with recurrent skin infections in the year before treatment, but no one had any infections in the follow-up period.

We used lymphoscintigraphy to quantitate any change in lymph flow. Before ADRC transplantation, MTT was 63.4 ± 26.8 min on the lymphedema arm and 5.4 ± 2.6 min on the contralateral healthy arm. Twelve months following treatment, MTT was 60.7 ± 36.8 min and 7.9 ± 3.0 min on the lymphedema arm and the contralateral healthy arm, respectively. There was a clear significant difference between the two arms both before and after treatment (Figure 2A and B, $p = 0.0020$). The group difference between pre- and postoperative MTT on the lymphedema arm was insignificant ($p = 0.6884$) (Figure 2C), whereas on the healthy arm, there was a significant increase in MTT ($p = 0.0006$) (Figure 2D).

No serious adverse events were noted. Minor short-term adverse events have been reported previously [5]. During the study period, one patient was diagnosed with a contralateral nonpalpable breast cancer as part of routine mammography screening 10 months following ADRC injection. No episodes of recurrence were detected.

Discussion

In this study, we aimed to examine the feasibility and safety of ADRC transplantation combined with fat grafting for treating BCRL. The treatment resulted in significant overall improvement in patient-reported outcome measures. Importantly, the procedure was safe even in the setting of previous cancer in the axillary region. Another benefit was that none of the four patients with recurrent skin infections experienced any infections in the 12 month follow-up period, which is similar to results achieved by microsurgical procedures [17].

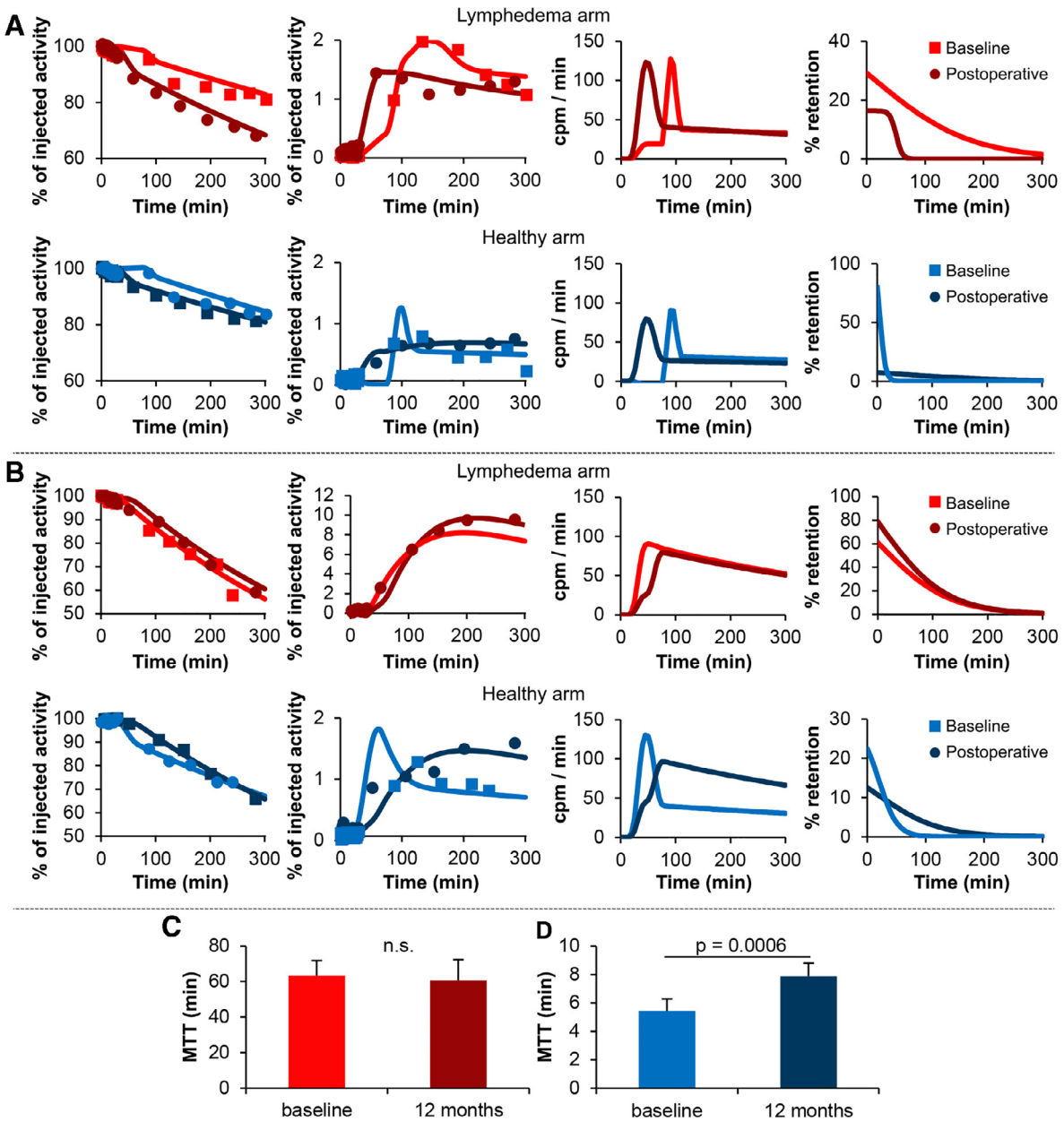

Figure 2 Change in lymphoscintigraphy parameters.
(A) The graphs illustrate representative results from a patient with improvement in the quantitative measure of lymph function mean transit time (MTT). The first graphs (left) illustrate the time-activity curve from the injection depot (red: lymphedema arm, blue: healthy arm). The second graphs (middle left) show the time-activity curve of the arm. The third graphs (middle right) show the resulting input function modeling the amount of activity entering the arm from the injection depot. The fourth graphs (right) show the retention function calculated based on the previous graphs in which the area under the curve corresponds to MTT. There is a clear reduction in the area under the curve for this patient, who no longer used any conservative management and felt great relief regarding the patient-reported outcomes. (B) The graphs illustrate representative results from a patient without any improvement in the MTT estimation. This patient had a decrease in arm volume and improvement in patient-reported outcomes, but this decrease did not correspond to any noteworthy change in MTT. (C) There was no significant difference in mean MTT on the lymphedema arm before and after treatment (results shown as means ± SEM). (D) There was a small but significant increase in MTT on the healthy arm after treatment (results shown as mean ± SEM).

The positive results were not reflected in the arm volume measurements. One explanation for this could be that patients were already in a stable phase with physiotherapeutic management, and the excess volume was at least to some extent due to chronic changes. The majority of patients had very limited pitting and were patients with stage II ISL [6]. Subgroup analysis revealed a tendency for better results for patients with stage I ISL in line with previous studies of microsurgical procedures, thus suggesting better efficacy for lower stages [18]. In addition, conservative management

is a known confounder when treating lymphedema, as volumetric changes can be attributed to this treatment rather than the surgical procedure [19].

The lack of clear objective measures to document a beneficial effect of therapeutic procedures has limited the translation of microsurgical procedures [20,21]. This is partly due to a lack of accepted quantitative measures for lymph drainage. The only previous lymphoscintigraphic results following cell therapy have been reported by Quián et al. [22], who described two cases of lower extremity lymphedema following multiple sclerosis (MS)-mesenchymal stem cell (MSC) therapy. After cell therapy, the authors demonstrated increased activity in proximal lymph nodes and greater extent of dermal back flow, which was interpreted as improvement. However, this evaluation was merely qualitative. We used quantitative lymphoscintigraphy to estimate MTT to evaluate the lymph drainage following ADRC injection. We found no change in mean MTT following ADRC treatment on the lymphedema arm, whereas we showed a slight increase (worsening) in the healthy arms. We are yet to speculate whether this worsening was due to a systemic reaction to the treatment or merely expresses inherent variability of the method. Our comparisons were limited by the fact that in two cases, the preoperative MTT was not accurately estimated, and only a minimum MTT value was estimated, thereby resulting in a "false" low preoperative MTT. Consequently, we may have underestimated the improvement in these two cases, both of whom had much faster MTT postoperatively. The varying results between the patients could indicate different responses to the treatment or represent an inherent insecurity in the reproducibility of the MTT estimation. The very small, although significant, changes on the healthy side suggest that the MTT estimation is very reproducible, but further studies need to document this. Overall, our results fit well with the qualitative interpretations of the scintigraphies, which did not show any major differences pre- and postoperatively.

Our procedure of ADRC-enriched fat grafting differed from the usually described method, where the ADRCs and fat graft are mixed before injection to secure a proper mix of the two components [23]. Instead, we opted to first inject the lipoaspirate and later the same day inject the ADRCs. This was performed purely for logistic reasons to avoid a prolonged general anesthesia and occupation of the operating room. It can be speculated whether this approach hampered the effect of the treatment. To our knowledge, these two approaches have not previously been compared. Further studies are needed to examine whether this is of importance.

The main limitations of our study were the lack of a control group and the low number of included patients. In general, lymphedema is either stable or worsens with time but very rarely improves without additional intervention, which means that any improvement is likely due to the given intervention [24]. However, the lack of a control group and the open-label design lead to a high risk of bias when evaluating the outcome. Our subgroup analysis was limited due to the low number of patients, but it did at least hint at how patient selection for future trials could be optimized, in that patients with stage I ISL seemed more likely to have a positive outcome. It will be interesting to follow-up these patients further and, if possible, offer retreatment, as previous studies have suggested a linear relationship between fat grafting and clinical improvement in radiation-induced tissue damage [25].

In conclusion, results from this study suggest that autologous ADRC transplantation together with fat grafting is safe with possible long-term efficacies. The use of adipose tissue as the source of autologous noncultured adult stem cells for BCRL treatment is appealing, as it can be obtained in large quantities with minimal discomfort and allow for a safe and minimally invasive surgical procedure. The next step toward routine clinical translation is to perform a randomized, blinded, placebo-controlled trial. It is important to document long-term safety in the transition toward the clinical use of ADRCs [26].

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Conflicts of interest

There were no conflicts of interest related to this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2018.09.007.

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