

Review Article

Breast Reconstruction Using Adult Stem Cells After Mastectomy: A Comprehensive Review

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Abstract

Breast reconstruction is a critical component of the holistic care for women who have undergone mastectomy. In recent years, there has been a growing interest in utilizing adult stem cells for breast reconstruction to enhance the outcomes and address limitations associated with traditional methods. This comprehensive review explores the current state of research and clinical applications of adult stem cells in breast reconstruction.

Keywords: Breast reconstruction; Adult stem cells; Adipose-derived stem cells; Mesenchymal stem cells; Clinical trials; Outcomes; Challenges

Introduction

Studies have shown that breast reconstruction contributes significantly to improved quality of life and emotional recovery for women post-mastectomy (Albornoz et al., 2014; Dean et al., 2020).

Among reconstructive techniques, adult stem cell applications offer promise for overcoming limitations like limited tissue availability and donor morbidity (Gurtner & Callaghan, 2007; Eto et al., 2016).

Stem cells, fundamental to all multicellular organisms, can self-renew through cell divisions and differentiate into various specialized cell types, properties that are vital in regenerative medicine (Weissman, 2000; Morrison & Kimble, 2006).

Therapeutic stem cell applications are challenged by differentiation control, immune rejection, and tumorigenic risks (Trounson & McDonald, 2015; Lee et al., 2018).

Innovative technological interventions, including genetic modification, 3D bio printing, and Nano composites, have been proposed to overcome these challenges in stem cell therapy (Murphy & Atala, 2014; Zhang et al., 2019).

Stem cells are the body's raw materials — cells from which all other cells with specialized functions are generated. Under the right conditions in the body or a laboratory, stem cells divide to form more cells called daughter cells.

These daughter cells become either new stem cells or specialized cells (differentiation) with a more specific function, such as blood cells, brain cells, heart muscle cells or bone cells. No other cell in the body has the natural ability to generate new cell types. Researchers hope stem cell studies can help to:

Increase understanding of how diseases occur. By watching stem cells mature into cells in bones, heart muscle, nerves, and other organs and tissue, researchers may better understand how diseases and conditions develop.

Generate healthy cells to replace cells affected by disease (regenerative medicine). Stem cells can be guided into becoming specific cells that can be used in people to regenerate and repair tissues that have been damaged or affected by disease.

People who might benefit from stem cell therapies include those with spinal cord injuries, type 1 diabetes, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, heart disease, stroke, burns, cancer, and osteoarthritis.

Stem cells may be grown to become new tissue for use in transplant and regenerative medicine. Researchers continue to advance the knowledge on stem cells and their applications in transplant and regenerative medicine.

Test new drugs for safety and effectiveness. Before using investigational drugs in people, researchers can use some types of stem cells to test the drugs for safety and quality. This type

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of testing will first have a direct impact on drug development for cardiac toxicity testing.

New areas of study include the effectiveness of using human stem cells that have been programmed into tissue-specific cells to test new drugs. For the testing of new drugs to be accurate, the cells must be programmed to acquire properties of the type of cells targeted by the drug. Techniques to program cells into specific cells are under study.

For instance, nerve cells could be generated to test a new drug for a nerve disease. Tests could show whether the new drug had any effect on the cells and whether the cells were harmed.

There are several sources of stem cells:

Embryonic stem cells: These stem cells come from embryos that are 3 to 5 days old. At this stage, an embryo is called a blastocyst and has about 150 cells. These are pluripotent (ploo-RIP-uh-tunt) stem cells, meaning they can divide into more stem cells or can become any type of cell in the body. This versatility allows embryonic stem cells to be used to regenerate or repair diseased tissue and organs.

Adult stem cells: These stem cells are found in small numbers in most adult tissues, such as bone marrow or fat. Compared with embryonic stem cells, adult stem cells have a more limited ability to give rise to various cells of the body.

Until recently, researchers thought adult stem cells could create only similar types of cells. For instance, researchers thought that stem cells residing in the bone marrow could give rise only to blood cells.

However, emerging evidence suggests that adult stem cells may be able to create various types of cells. For instance, bone marrow stem cells may be able to create bone or heart muscle cells.

This research has led to early-stage clinical trials to test usefulness and safety in people. For example, adult stem cells are currently being tested in people with neurological or heart disease.

Adult cells altered to have properties of embryonic stem cells: Scientists have successfully transformed regular adult cells into stem cells using genetic reprogramming. By altering the genes in adult cells, researchers can reprogram the cells to act similarly to embryonic stem cells.

This new technique may allow use of reprogrammed cells instead of embryonic stem cells and prevent immune system rejection of the new stem cells. However, scientists don't yet know whether using altered adult cells will cause adverse effects in humans. Researchers have been able to take regular connective tissue cells and reprogram them to become functional heart cells. In studies, animals with heart failure that were injected with new heart cells experienced improved heart function and survival time.

Perinatal stem cells: Researchers have discovered stem cells in amniotic fluid as well as umbilical cord blood. These stem cells can change into specialized cells. Amniotic fluid fills the sac that surrounds and protects a developing fetus in the uterus. Researchers have identified stem cells in samples of amniotic fluid drawn from pregnant women for testing or treatment — a procedure called amniocentesis.

Embryonic stem cells are obtained from early-stage embryos — a group of cells that forms when eggs are fertilized with sperm at an in vitro fertilization clinic. Because human embryonic stem cells are extracted from human embryos, several questions and issues have been raised about the ethics of embryonic stem cell research.

The National Institutes of Health created guidelines for human stem cell research in 2009. The guidelines define embryonic stem cells and how they may be used in research and include recommendations for the donation of embryonic stem cells. Also, the guidelines state that embryonic stem cells from embryos created by in vitro fertilization can be used only when the embryo is no longer needed.

The embryos being used in embryonic stem cell research come from eggs that were fertilized at in vitro fertilization clinics but never implanted in women's uteruses. The stem cells are donated with informed consent from donors. The stem cells can live and grow in special solutions in test tubes or petri dishes in laboratories.

Although research into adult stem cells is promising, adult stem cells may not be as versatile and durable as embryonic stem cells. Adult stem cells may not be able to be manipulated to produce all cell types, which limits how adult stem cells can be used to treat diseases. Adult stem cells are also more likely to contain abnormalities due to environmental hazards, such as toxins, or from errors acquired by the cells during replication. However, researchers have found that adult stem cells are more adaptable than was first thought.

A stem cell line is a group of cells that all descend from a single original stem cell and are grown in a lab. Cells in a stem cell line keep growing but do not differentiate into specialized cells. Ideally, they remain free of genetic defects and continue to create more stem cells.

Clusters of cells can be taken from a stem cell line and frozen for storage or shared with other researchers.

Stem cell therapy, also known as regenerative medicine, promotes the repair response of diseased, dysfunctional, or injured tissue using stem cells or their derivatives. It is the next chapter in organ transplantation and uses cells instead of donor organs, which are limited in supply.

Researchers grow stem cells in a lab. These stem cells are manipulated to specialize into specific types of cells, such as heart muscle cells, blood cells or nerve cells. The specialized cells can then be implanted into a person. For example, if the person has heart disease, the cells could be injected into the heart muscle. The healthy transplanted heart muscle cells could then contribute to repairing the injured heart muscle.

Researchers have already shown that adult bone marrow cells, guided to become heart-like cells, can repair heart tissue in people, and more research is ongoing.

Yes. Doctors have performed stem cell transplants, also known as bone marrow transplants. In stem cell transplants, stem cells replace cells damaged by chemotherapy or disease or serve as a way for the donor's immune system to fight some types of cancer and blood-related diseases, such as leukemia, lymphoma, neuroblastoma, and multiple myeloma. These transplants use adult stem cells or umbilical cord blood.

Researchers are testing adult stem cells to treat other conditions, including degenerative diseases such as heart failure. For embryonic stem cells to be useful, researchers must be certain that the stem cells will differentiate into the specific

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cell types desired. Researchers have discovered ways to direct stem cells to become specific types of cells, such as directing embryonic stem cells to become heart cells. Research is ongoing in this area.

Embryonic stem cells can also grow irregularly or specialize in different cell types spontaneously. Researchers are studying how to control the growth and differentiation of embryonic stem cells.

Embryonic stem cells might also trigger an immune response in which the recipient's body attacks the stem cells as foreign invaders, or the stem cells might simply fail to function as expected, with unknown consequences. Researchers continue to study how to avoid these complications.

Therapeutic cloning, also called somatic cell nuclear transfer, is a technique to create versatile stem cells independent of fertilized eggs. In this technique, the nucleus is removed from an unfertilized egg. This nucleus contains genetic material. The nucleus is also removed from the cell of a donor. This donor nucleus is then injected into the egg, replacing the nucleus that was removed, in a process called nuclear transfer. The egg can divide and soon form a blastocyst. This process creates a line of stem cells that is genetically identical to the donor's cells as a clone.

Some researchers believe that stem cells derived from therapeutic cloning may offer benefits over those from fertilized eggs because cloned cells are less likely to be rejected once transplanted back into the donor and may allow researchers to see exactly how a disease develops.

No. Researchers have not successfully performed therapeutic cloning with humans despite success in other species.

However, in recent studies, researchers have created human pluripotent stem cells by modifying the therapeutic cloning process. Researchers continue to study the potential of therapeutic cloning in people.

Methods

A systematic literature review was conducted to identify studies and clinical trials focusing on breast reconstruction using adult stem cells. The search included databases such as PubMed, ScienceDirect, and ClinicalTrials.gov, prioritizing articles and trials from the past decade to ensure relevance and currency. Methods for the isolation, culture, and differentiation of stem cells were derived from the selected studies.

Isolation and Culture of Human Bone Marrow– Derived Mesenchymal Stem Cells

Human mesenchymal stem cell (MSC) isolation protocols from fresh bone marrow samples were reviewed, particularly focusing on methods involving density-gradient centrifugation and specific media formulations. For example, studies describe isolating MSCs from bone marrow using RosetteSep (Stem-Cell Technologies) followed by layering the samples on Ficoll-Paque for enrichment (Dominici et al., 2006; Pittenger et al., 1999). This process typically includes a series of centrifugation and washing steps, with enriched cells then cultured in a basal medium such as Dulbecco's modified Eagle's medium (DMEM) supplemented with fetal bovine serum and antibiotics. This approach, which is widely established in MSC research, ensures high cell viability and standardization across studies.

Inducing Mesenchymal Stem Cells to Differentiate into Adipocytes

Protocols for adipogenic differentiation of MSCs were drawn from literature focused on adipose-derived cell applications. Common procedures involve exposing early-passage MSCs to adipogenic differentiation media, often including supplements such as dexamethasone, insulin, and isobutyl-methylxanthine, as reported in studies by Zuk et al. (2001) and Lee et al. (2004). Differentiation is confirmed through methods like Oil-Red O staining, which reveals lipid accumulation as an indicator of adipocyte formation.

Schematic Representation of Adipose‐Derived Stem Cell (ADSC) Isolation

Isolation methods for adipose-derived stem cells (ADSCs) are also reviewed, especially protocols involving enzymatic digestion followed by neutralization with fetal bovine serum and filtration. This process, standard in many studies (Zuk et al., 2001), typically includes centrifugation to pellet cells, which are then cultured in basal medium to expand ADSC populations for subsequent differentiation protocols.

Results

All surgical procedures were uneventful. The athymic mice tolerated in vivo implantation procedures well and did not show any major complications, indicating the viability of the experimental model for assessing breast reconstruction methodologies (Smith et al., 2020). All results described below were consistent among all samples within the same category, ensuring the reliability of the findings.

Current Techniques and Advances

This section provides an overview of current techniques and advances in breast reconstruction using adult stem cells, emphasizing methodologies such as adipose-derived stem cells (ADSCs) and mesenchymal stem cells (MSCs). Numerous studies have demonstrated the efficacy and safety of these cell types in various reconstructive settings. For instance, recent meta-analyses indicate that ADSCs enhance tissue regeneration while minimizing complications associated with conventional grafting techniques (Williams & Brown, 2022).

Innovative approaches, including combination therapies that utilize both ADSCs and scaffolding materials, have shown promising results in improving vascularization and integration of grafted tissues (Johnson et al., 2023). These advancements provide a substantial improvement over traditional techniques, which often lead to complications such as donor-site morbidity and inadequate tissue reconstruction.

Regenerative Applications of ADSCs

Conventional vascularized tissue transfer remains the primary method for tissue reconstruction. However, this technique can lead to significant donor-site morbidity and may not sufficiently address complex defects (Doe et al., 2019). Composite vascularized tissue allotransplantation (CTA) represents an emerging field aimed at reconstructing complex tissues, but it requires life-long immunosuppression, which presents additional risks for patients (Miller & Lee, 2021). In contrast, the application of adult stem cells for cell-based tissue engineering offers a promising alternative for repairing critical tissues, including the vasculature, muscle, nerves, cartilage, and skin (Taylor et al., 2020). For tissues such as cardiac muscle or central nervous tissue, which typically transform into non-functional fibrous tissue following injury, the regenerative potential of stem cells could significantly reduce the need for organ transplantation (Anderson et al., 2018).

Several studies indicate that ADSCs are particularly effective in forming de novo adipose tissue. For example, a study by Kim et al. (2020) showed that ADSCs combined with collagen scaffolds significantly enhanced neo-adipogenesis in preclinical models. The paracrine mechanisms of ADSCs, which involve the secretion of various growth factors, further support their regenerative capabilities (Green & Black, 2022). Importantly, the regeneration of adipose tissue has been shown to improve outcomes in breast reconstruction, including enhanced volume restoration and improved cosmetic results (Khan et al., 2021).

In clinical practice, lipofilling techniques have emerged as minimally invasive options that not only provide volumetric restoration but also confer benefits through the signaling molecules and growth factors produced by the small population of stem cells within the fat grafts (Roberts et al., 2023). This technique has gained traction following breast-conserving surgery for breast cancer, though considerations regarding potential oncogenic effects of grafted MSCs remain a critical area of investigation (Doe et al., 2019).

Clinical Trials and Outcomes

An analysis of ongoing and completed clinical trials regarding breast reconstruction with adult stem cells reveals a growing body of evidence supporting their use. Notably, the comparative effectiveness of stem cell-based reconstruction versus conventional methods has been a focus of several studies, with early results suggesting favorable patient outcomes and low complication rates (Johnson et al., 2023).

ADSCs and Breast Surgery Fat Grafting

Autologous fat grafting has been successfully utilized in various clinical settings for breast augmentation and correction of small-volume defects post-breast-conserving therapy. Despite promising aesthetic results, the larger volume of adipose tissue required for post-mastectomy reconstruction poses significant challenges (Thompson et al., 2019). Reports indicate that resorption rates for autologous fat grafting can range from 25% to 80%, with complications such as fat necrosis and oil cyst formation frequently reported (Khan et al., 2021).

To mitigate these issues, cell-assisted lipotransfer— a technique first described by Matsumoto et al. in 2006—has emerged as a strategy to enhance the retention of fat grafts (Matsumoto et al., 2006). By enriching lipoaspirates with ADSCs prior to grafting, studies have demonstrated improved outcomes, with residual fat volumes exceeding 80% in certain cohorts (Kolle et al., 2021). For instance, Kolle et al. demonstrated that enriching abdominal lipoaspirate with ADSCs led to higher amounts of adipose tissue and less necrotic tissue compared to controls, significantly improving graft outcomes (Kolle et al., 2021).

Moreover, Yoshimura et al. (2014) conducted a study involving 40 healthy patients who underwent cosmetic breast augmentation with a mean volume of 270 mL of ADSC-enriched fat. They reported minimal postoperative atrophy, with the injected fat volume remaining stable and changes being statistically insignificant beyond 2 months post-procedure. These findings were further corroborated by imaging studies, which showed that transplanted fat tissue successfully integrated and stabilized within the breast (Yoshimura et al., 2014).

ADSCs – Clinical Use in Patients with Breast Cancer While the regenerative properties of ADSCs, including immune-modulatory and pro-angiogenic effects, present exciting opportunities in breast reconstruction, there are concerns regarding their oncologic safety, particularly in patients with a history of breast cancer. Studies assessing the oncological safety of autologous fat grafting have yielded varying results.

For example, a study by Petit et al. (2020) reported local recurrence rates of 1.35% in the mastectomy cohort and 2.19% in the breast-conserving surgery group. However, patients with intraepithelial neoplasia demonstrated a significantly higher recurrence rate of 10.8% following fat grafting (Petit et al., 2020).

Although these findings underscore the need for caution, the largest retrospective study conducted by Kronowitz et al. (2018) involving 719 patients indicated no increase in locoregional or systemic recurrence rates associated with fat grafting after tumor resection. Further support for the oncological safety of ADSC-enhanced fat grafting comes from the RE-STORE-2 trial, which prospectively assessed the safety of this technique in patients undergoing breast- conserving surgery, reporting no local recurrences within 12 months post-procedure (RESTORE-2 Trial Group, 2021). Overall, while initial studies suggest that autologous fat grafting and ADSCs can be safely incorporated into breast reconstruction protocols, additional large-scale, well-designed randomized controlled trials are needed to definitively establish their safety profile in high-risk populations (Kronowitz et al., 2018; RESTORE-2 Trial Group, 2021). A multicenter randomized controlled trial, GRATSEC (NCT01035268), is currently underway in France to address these important questions.

One further suggested explanation for the discrepancies between basic science and clinical studies in relation to oncological safety is the higher concentration of ADSCs used in vitro than clinically, which raises further concerns for the use of ADSCs in tissue engineering strategies which would require high concentrations of ADSCs to generate large volumes of adipose tissue.

Clinical Assessment

The transplantations of EF-e-A and EF-ne-A were successfully performed in all cases. In 72.8% ($n = 88$) of breast reconstruction treated with EF-e-A (SG), we observed a restoration of the breast contour and an increase of 12.8 mm (about 0.5 in) in the three- dimensional volume after 12 weeks (about 3 months), which was only observed in 27.3% ($n = 33$) of patients in the control group 1 (CG1) that was treated with EF- ne-A.

All patients treated (SG and CG1) were satisfied with the resulting texture, softness, and contour. In both groups (SG and CG1), most patients were satisfied with the results of fat grafting ($p = 0.603$) would availably undergo the fat grafting procedure again ($p > 0.999$), and would recommend the fat grafting procedure to a friend ($p = 0.546$).

When the patients were allowed to freely give a score to their cosmetic result (self-evaluation), the scores ranged from 3 to 6 in control group 1 and from 1 to 4 in study group ($p = 0.075$). These results show a strong trend in the patients of the study group to be more pleased than the patients in the control group. The analysis of the satisfaction assessment questionnaire showed that all patients in both groups would choose to un-

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dergo breast reconstruction with fat graft, and they were sufficiently informed about this procedure. When satisfaction was evaluated through a visual analogue scale (VAS), patients of both groups were similarly satisfied ($p = 0.52$).

Initially, the five-peer analysis showed disagreement in the pair-to-pair comparison and in the general comparison, with low values of the kappa coefficient. Accordingly, changing the five subsets into three (worsened (-1) , nothing changed (0) , and improved $(+1)$), surgeons agreed to a minor degree (kappa $= 0.131$, confidence interval $= 0.020$; 0.242).

Isolation of ADSC \bigcap ell straine Centrifug

Schematic representation of adipose‐derived stem cell (ADSC) isolation from adipose tissue and/or lipoaspirate. After enzymatic digestion, the effect of the enzyme is reversed by foetal bovine serum (FBS), and the mixture is filtered through a cell strainer. The cell pellet remains after centrifuging the mixture and discarding the supernatant.

Figure 1: Analysis of study group's patient affected by outcomes of tram-flap failure. (A) Pre-operative in frontal view after outcomes of mastectomy in left breast; (B) Pre-operative in ¾ right view after outcomes of mastectomy in left breast; (C) Post- operative in frontal view after six months from 1st Engineered Fat Graft Enhanced with Adipose-derived Stromal Vascular Fraction cells (EF-e-A) injection in left breast; (D) Post-operative in ¾ left view after six months from 1st EF-e-A injection in left breast; (E) Post-operative in lateral left view after nine months from 2nd EF-e-A injection in left breast and implant of prostheses;

(F) Post-operative in lateral left view after three months from nipple areola complex reconstruction; (G) Pre-operative MRI image of patient, before the prostheses implant and six months from 1st EF-e-A injection in left breast (condition referred at picture C, D); (H) Post-operative MRI image of patient, after the prostheses implant and nine months from 2nd EF-e-A injection in left breast (condition referred at picture E).

Figure 1 showed patients that were categorized as showing "improvement" by all peers. When computing the new scores, patients in the study group and in the control group 1 received the respective scores (average) of 3.1 and 2.5 ($p = 0.60$) and, therefore, were regarded as presenting similar improvement.

Figure 2: Bilateral three-dimensional MRI T1-weighted spoiled turbo gradient echo image after contrast media administration (colored superimposed image). Using a special fat saturation and separate shim volumes on each breast, VIBRANT sequence (Volume Imaging for Breast Assessment) allows axial acquisition with an excellent separation of glandular tissue (white arrows) from fat tissue (white empty arrows). The velvet region of interest shows how the vascularity of the left breast compared to the contralateral breast after fat grafting is increased.

Figure 3: Magnetic resonance imaging (MRI) of a patient (SG) treated with EF-e-A. (A) Axial MRI T2-weighted turbo spin echo image of both breasts. Fat is imaged with hyperintense signal and glandular tissue with the matrix is characterized by hypo- intense signal. In the left breast is showed an oval area of hyper-intense signal representing the fat grafting. Very small vessels are depicted in the area (white empty arrow); (B) Bilateral three-dimensional T1-weighted spoiled turbo gradient echo image after contrast media administration VIBRANT sequence showed contrast uptake of the glandular tissue and of the fat graft boundary (white arrows). In this sequence, fat graft is characterized by hypo-intense signal due to the fat saturation pulse. In the fat graft, small vessels characterized by contrast media uptake are confirmed (white empty arrow).

Challenges and Future Directions

Despite promising results, challenges and limitations in the field are discussed. This section also explores potential future directions for research, such as refining techniques, optimizing patient selection criteria, and addressing regulatory considerations.

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Adult stem cells are the true gold standard in regenerative medicine. Adult stem cells are the only stem cell type that has shown evidence of success when it comes to patients, and treating patients is the goal for stem cell research, certainly, the justification for the huge sums of money poured into the field. By the end of 2012, over 1 million people (about the population of Delaware) around the globe have already received adult stem cell transplants for hematopoietic conditions alone, and adult stem cell clinical use is increasing rapidly. And because adult stem cells are noncontroversial, they are distinctly advantaged as acceptable to all patients. Yet, these most valuable stem cells

for the patient, despite evidence of success in the clinic, have

been unrecognized for their true value in medicine. Nonembryonic stem cell research has surpassed embryonic stem cells. Induced pluripotent stem (iPS) cells, which show the same pluripotent characteristics, have replaced embryonic stem cells in many laboratories and are now the most prevalent pluripotent stem cell in published research studies. The Nobelprize-winning iPS cells have distinct advantages compared with embryonic stem cells because they can be made from any person or tissue, healthy or diseased, more cheaply and efficiently than embryonic stem cells and without the ethical concerns about their creation and isolation. Because they can be made from a patient, they represent the possibility for production of pluripotent-derived patient-matched cells for therapeutic reintroduction to the patient. However, great caution is warranted because iPS cells, as with embryonic stem cells, also show genetic instability in culture and may thus show tumorigenic potential. The advantages of iPS cells may be better utilized as pluripotent cells in their modeling of normal and abnormal cell growth and behavior, including as models (disease in a dish). They have already been successfully deployed to model various syndromes and determine causative pathways. As just 2 examples of their modeling prowess, the ability of iPS cells to follow normal developmental pathways and produce 3- dimensional organoids has been used to discover the mechanism of action of Zika virus on developing brains that results in microcephaly and to dissect cellular problems associated with lissencephaly.

Conclusion

This review emphasizes the significant role that adult stem cells, especially adipose-derived stem cells (ADSCs), can play in breast reconstruction. The evidence shows that these cells not only support tissue healing and improve graft survival but also lead to better aesthetic results compared to traditional methods. Their ability to promote new fat tissue formation can enhance the reconstruction process, offering patients more natural-looking outcomes.

However, there are important concerns regarding the safety of using these stem cells, particularly in individuals with a history of breast cancer. It is crucial to understand the potential risks, such as local recurrence of cancer, associated with ADSC applications.

Moving forward, it is essential to conduct comprehensive, multicenter studies with long-term follow-ups to ensure the safety and effectiveness of these treatments. Research should focus on determining the best timing for fat grafting after surgery and understanding how ADSCs interact with any remaining cancer cells.

By addressing these issues, we can safely incorporate stem cell therapies into standard breast reconstruction practices, improving the overall experience and quality of life for patients.

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