IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Autologous fat grafting to the breast has been used as an adjunct to reconstructive breast surgery, for post-mastectomy pain and in irradiated skin. Adipose derived stem cells have been proposed as a supplement to the fat graft in an attempt to improve graft survival.

Adipose Tissue Physiology in Fat Grafting

Harvesting of adipose tissue by liposuction is relatively easy, minimally invasive, and associated with minimal patient discomfort and morbidity. Small amounts (100-200 mL) can be obtained under local anesthesia. The most common technique, called the Coleman technique, also involves a purification step which involves centrifugation to remove blood, fluid and ruptured adipocytes.

Adipose tissue is a highly vascularized tissue, and adipocytes are in direct contact with adjacent capillary vessels. In free fat grafting, direct diffusion of nutrients from plasma in the surrounding bed and subsequent revascularization usually occurs within 48 hours and are essential for graft survival. If the local environment does not undergo revascularization, the grafted fat tissue eventually undergoes necrosis, one complication after fat grafting. Other complications include oil cyst formation, indurations in either the subcutis or breast parenchyma, calcification, and severe breast deformity.¹
**Indications for autologous fat grafting to the breast**

Autologous fat grafting to the breast has been proposed for indications which include breast augmentation and following oncologic surgery. Proposed indications following oncologic surgery include as an adjunct to reconstruction post mastectomy or lumpectomy for contour deformities and improved shape and volume of the breast, for post mastectomy pain syndrome (neuropathic pain), and for irradiated skin to soften the skin and restore it to non-irradiated appearance and consistency.

**Adipose-derived Stem Cells**

Stem cell biology, and the related field of regenerative medicine, involves multipotent stem cells that exist within a variety of tissues, including bone marrow and adipose tissue. Studies have shown that 1 gram of adipose tissue yields approximately $5 \times 10^3$ stem cells, which is up to 500 times greater than the number of mesenchymal stem cells in 1 gram of bone marrow. Stem cells, because of their pluripotentiality and unlimited capacity for self-renewal, offer promise for tissue engineering and advances in reconstructive procedures. Adipose tissue in particular represents an abundant and easily accessible source of adipose-derived stem cells (ADSCs), which can differentiate along multiple mesodermal lineages. ADSCs may allow for improved graft survival and generation of new fat tissue after transfer from another site.

This identification of several potentially beneficial therapeutic properties of ADSC has led to proposed novel techniques of fat grafting in conjunction with ADSC therapy for breast fat grafting, including the differentiation of ADSC into adipocytes as a reservoir for adipose tissue turnover, the differentiation of ADSC into endothelial cells and the subsequent increase in blood supply to the grafted fat tissue, thereby decreasing the rate of graft resorption, the release of angiogenic growth factors by ADSC and the induction of angiogenesis, protection of the graft from ischemic reperfusion injury by ADSC, and acceleration of wound healing at the recipient site.

**Regulatory Status**

A point-of-care system is available for concentrating ADSC from mature fat. The Celution™ system (Cytori Therapeutics, Inc.) is designed to transfer a patient’s own adipose tissue from one part of the body to another in the same surgical procedure. The system received 510(k) marketing clearance from the U.S. Food and Drug Administration as a cell saver device. The system is cleared for the collection, concentration, washing and re-infusion of a patient’s own cells for applications that may include, but are not limited to, cardiovascular, plastic and reconstructive, orthopedic, vascular, and urological surgeries and procedures.

*Note:* This policy does not address free flap autologous fat grafting with microvascularization. Further, this policy does not address the use of autologous fat tissue in aesthetic breast augmentation (i.e., cosmesis).

**MEDICAL POLICY CRITERIA**

The use of autologous fat grafting to the breast, with or without adipose-derived stem cells is considered investigational.
SCIENTIFIC EVIDENCE

Literature Review

In order to understand the impact on health outcomes of fat grafting to the breast, with or without adipose-derived stem cells, prospective clinical trials are needed, comparing fat grafting to standard reconstructive procedures. These comparisons are necessary in order to understand the safety and efficacy of the procedures and to determine whether fat grafting offers advantages over conventional surgical procedures with respect to complications, durability, post-procedure ability to detect cancer, and cosmesis.

Autologous Fat Grafting in Breast Reconstruction

Systematic Reviews

Several systematic reviews have been published on autologous fat grafting in breast reconstruction. Below is a summary of key reviews that include similar nonrandomized studies.

Agha et al. (2014) conducted a comprehensive, good quality systematic review of the evidence with meta-analysis of oncologic outcomes. The review evaluated women with breast cancer undergoing reconstruction after surgery. A total of 35 nonrandomized studies were included (3624 patients and 4138 breasts) with a median follow-up of 18 months. No RCTs were identified for inclusion in the review. Most studies were determined to be of low quality with only six cohort studies and three comparative studies assessed as moderate quality. It is important to note that there were differences in techniques, patient populations, and indications across studies. Post-operative complications were 7.3% with fat necrosis (4.4%) being the most common. The weighted mean cancer recurrence rate at a median 24.6 months was 4.4%. For the moderate quality studies only, there were no significant difference in cancer recurrence rates for autologous fat grafting compared to control groups (5.3% compared to 4.7%, p=0.10). Biopsy of subsequent breast lumps was needed in 2.7% of patients. The interval mammogram was needed in 11.5% of patients. The authors concluded that high quality studies are needed that report long term data for oncological outcomes and the current evidence review is limited by the low quality of studies with methodological limitations.

Tsoi et al. (2014) compared the safety of tissue expander/implant reconstruction with that of autologous abdominal tissue reconstruction in a systematic review. Fourteen observational studies were identified that included more than 3000 reconstructed breasts. Significant differences were found between these two approaches. The relative risk associated with reconstructive failure favored autologous abdominal tissue (relative risk, 0.14; 95 percent CI, 0.06 to 0.32; I = 0 percent). Surgical-site infection was significantly lower in autologous abdominal tissue reconstruction compared with tissue expander/implant (relative risk, 0.37; 95 percent CI, 0.25 to 0.55; I = 0 percent), although skin or flap necrosis was higher in autologous abdominal tissue reconstruction compared with tissue expander/implant (relative risk, 2.79; 95 percent CI, 1.87 to 4.17). Studies were of low to moderate quality according to the Newcastle-Ottawa scale. The authors concluded that with the lack of long-term safety studies on different approaches to breast reconstruction, additional long-term comparative studies are needed to support evidence-based decision-making.

A 2013 systematic review by Krastev et al. examined the evidence of the oncological risks associated with autologous fat grafting in breast cancer patients. The review included trials with female patients who underwent either mastectomy or breast conserving therapy (BCT) and subsequent breast
reconstruction including autologous fat grafting. The oncologic safety of the fat grafting procedure was assessed by locoregional recurrence rates. The trials included one retrospective cohort study, one multicenter study of case series without controls, two smaller cohorts and several case series. Although 20 trials met the inclusion criteria for the review, only nine reported oncologic recurrence rates. The level of evidence was rated as low due to lack of control groups, lack of randomization, their retrospective nature and small sample sizes. Across the studies there was variation in invasive versus in situ carcinomas and the percentage of patients who underwent radiation therapy before fat grafting. The mean interval between surgery and fat grafting varied across studies between 1 and 6.5 years, and mean follow-up varied between 1 and 5 years. The largest study in the review by Petit et al. was a multicenter study which reported locoregional recurrence rates of 1.35% and 2.19% per year for the mastectomy and BCT groups, respectively. The authors of the systematic review stated that the highest level of evidence currently available on the oncologic safety of fat grafting to the breast is a retrospective cohort analysis by Petit et al. which was included in the review, and deemed to be level 2b evidence. The cohort analysis included 321 consecutive patients operated for a primary breast cancer between 1997 and 2008 who subsequently underwent fat grafting for reconstructive purpose. For each patient, two matched controls with similar characteristics were selected who had not undergone fat transfer. There were no significant differences between the fat grafting and control groups in locoregional or distant cancer recurrence. The authors of the systematic review concluded that it is still unclear whether fat grafting to the breast promotes locoregional recurrence, and that larger prospective trials with longer follow-up are needed.

In a 2013 critical review, authors critically assessed the current body of literature in fat grafting to provide a framework to guide application and comparison. Authors included 103 articles in their review; headings included donor site, effect of infiltration solution, harvest method, effect of centrifugation, reinjection method, supplementation, the role of adipose-derived stem cells, and scaffolding. Authors concluded that there is no consensus on the optimum technique of autologous fat grafting in both reconstructive and cosmetic surgery due to the array of research methods and short follow-up durations.

A 2012 systematic review by Claro et al. examined the clinical applicability and safety of autologous fat grafting to the breast for reconstruction by identifying clinical complications, radiographic changes and incidence of primary or recurrent breast cancer. Although the review also included patients who underwent fat grafting for augmentation, there were 41 studies that included 3646 patients who underwent grafting for reconstruction. The reconstruction was mainly for partial breast reconstruction and/or correction of breast deformities, but also included patients who underwent total breast reconstruction and for postradiation radiodermatitis. The majority of the studies were graded as low or very low quality. Complication results were not reported separately for the studies that included fat grafting for augmentation versus reconstruction. Clinical complications were 3.9% and consisted mainly of induration and/or palpable nodularity and radiographic abnormalities occurred in 13%, most commonly as cysts. Local recurrence of breast cancer was evaluated in three studies, of which only one was prospective. The three studies included 616 patients with a mean follow-up of 45.2 months. Fourteen recurrent cancers were reported (2.3%), all in women whose initial treatment was mastectomy. The authors concluded that fat grafting to the breast is associated with few complications with no evidence of interference with follow-up after treatment for breast cancer, and that the rate of breast cancer recurrence in the women who had fat grafting to the breast was similar to published rates for patients undergoing mastectomy who did not receive fat grafting, but that confirmation of the oncological safety awaits the results of controlled trials.

A 2012 literature review by Saint-Cyr and colleagues on the role of fat grafting in reconstructive and cosmetic breast surgery included articles published between 2001 and 2011. Due to the heterogeneity
of the studies, a formal meta-analysis was not completed. Out of 19 chosen studies, 11 had patients receiving autologous fat transplantation as an adjunct to breast reconstruction, five studies enrolled patients receiving the procedure for strictly cosmetic purposes, and three studies used fat grafting for both reconstructive and cosmetic purposes. In the studies included in the review, follow-up intervals ranged from 2 weeks to 19.1 years. The number of sessions employed per patient ranged from 1 to 7, with the intervals of time between sessions, when reported, ranging from 21 to 263 days. The review found it difficult to correlate patient or surgeon satisfaction with volume stability or complication rate as there was not a standardized method of documenting clinical success, postoperative volume stability, or follow-up intervals used to report complications; however, the majority of studies yielded results that were satisfactory or better. For fat grafting used in the setting of radiation (four studies), two studies reported a significant decrease in the LENT-SOMA scores in 95 to 100% of patients. Postoperative volume analysis was only performed in three studies. Postoperative infections, all managed with antibiotics, were reported in four of the studies. Among the 19 selected studies in the literature review, the methods used in the harvesting, processing, and injection of the adipose tissue varied widely. The authors of this review concluded that large prospective studies with well-defined follow-up measures are needed to more clearly demonstrate specific risks and answer questions concerning the amount of adipose resorption and long-term stability of the fat grafts used for reconstructive and cosmetic purposes.

**Randomized Controlled Trials**

There were no randomized controlled trials identified.

**Nonrandomized Studies**

There are a large number of nonrandomized studies, most of which were included in the previously summarized systematic reviews that contribute to the body of knowledge concerning autologous fat grafting and may be used to provide direction for future research. However, valid and reliable conclusions about the impact of autologous fat grafting on health outcomes cannot be reached from these studies due to methodological limitations and the lack of long-term outcomes.[10-19]

**Autologous Fat Grafting and the Use of Adipose-derived Stem Cells (ADSC)**

Pérez-Cano (2012) conducted a single-arm, prospective, multicenter clinical trial of 71 women who underwent breast conserving surgery for breast cancer and autologous adipose-derived regenerative cell (ADRC)-enriched fat grafting for reconstruction of defects ≤150 mL (the RESTORE-2 trial).[20] Trial endpoints included patient and investigator satisfaction with functional and cosmetic results and improvement in overall breast deformity at 12 months post-procedure. Female patients (18-75 years of age) presenting with partial mastectomy defects and without breast prosthesis were eligible. The RESTORE-2 protocol allowed for up to two treatment sessions and 24 patients elected to undergo a second procedure following the six-month follow-up visit. Of the 67 patients treated, 50 reported satisfaction with treatment results through 12 months. Sixty-one patients underwent radiation therapy as part of their treatment; two patients did not receive radiation and the status of radiation treatment was not known for the other 4 patients. Using the same metric, investigators reported satisfaction with 57 out of 67 patients. There were no serious adverse events associated with the ADRC-enriched fat graft injection procedure. There were no reported local cancer recurrences. The LENT-SOMA scale included investigator and patient assessment of post-radiation signs and symptoms. The investigators of the trial found that LENT-SOMA was insufficiently sensitive to adequately reflect the clinical improvements seen in the trial population. Patients with LENT-SOMA III and IV scores (most severe symptoms) were
excluded during screening, which may have contributed to the subtle LENT-SOMA score changes observed in the trial. The investigators reported improvement from baseline through 12 months in the degree of retraction or atrophy in 29 out of 67 patients, while 34 patients had no change and 4 patients reported worse symptoms. Post-radiation fibrosis at 12 months was reported as improved in 29 patients, while 35 patients had no change and 3 patients had worse symptoms. Management of atrophy was reported as improved in 17 patients, with 48 patients having no change and 2 patients reporting worse symptoms. Improvement in these measures reached statistical significance. The authors concluded that future comparative studies are needed to determine the incremental benefit of ADRC-enriched fat grafting as compared to traditional fat grafting in various clinical circumstances.

Kamakura and Ito (2011) reported on the use of ADSC enriched fat grafting for breast augmentation in a prospective, nonrandomized open-label study of 20 Japanese women.[21] After the adipose tissue was harvested by liposuction, it was processed in the Celution 800 System® to wash and isolate the adipose-derived regenerative cells and produce a fat graft enriched with the regenerative cells. Clinical outcomes measured included improvement in circumferential breast measurement from baseline state. There was improvement in circumferential breast measurement in all patients, and breast measurements were stable by 3 months after grafting. At 9 months, the mean breast measurement had increased 3.3 cm from preoperative measurements. The procedure was well-tolerated without any serious adverse events. Postoperative cyst formation was seen in 2 patients.

Yoshimura and colleagues (2008) reported on the development of a novel strategy known as cell-assisted lipotransfer (CAL), in which autologous ADSCs are used in combination with lipoinjection.[22] From 2003-2007, the group performed CAL in 70 patients: in the breast in 60 patients (including 8 who had breast reconstruction after mastectomy). They reported outcomes for 40 patients with healthy thoraxes and breasts who underwent CAL for purely cosmetic breast augmentation; patients undergoing breast reconstruction for an inborn anomaly or after mastectomy were not included. Nineteen of the 40 patients had been followed for more than 6 months, with a maximum follow-up of 42 months. The authors observed that the transplanted adipose tissue was gradually absorbed during the first 2 postoperative months, and the breast volume showed a minimal change thereafter. Final breast volume showed augmentation by 100 to 200 mL after a mean fat amount of 270 mL was injected. The difference in breast circumference (defined as the chest circumference at the nipple minus the chest circumference at the inframammary fold) had increased in all cases by 4 to 8 cm at 6 months. Cyst formation or microcalcification was detected in 4 patients. The authors concluded that their preliminary results suggest that CAL is effective and safe for soft tissue augmentation and superior to conventional lipoinjection but that additional study is necessary to further evaluate the efficacy of this technique.

Rigotti et al (2007) reported the results of a pilot study on the presence and effectiveness of ADSCs in 20 consecutive patients undergoing therapy for adverse effects of radiation treatment to the breast, chest wall or supraclavicular region, with severe symptoms or irreversible function damage (LENT-SOMA scale grade 3 and 4). LENT-SOMA is one of the most common systems to assess the late effects of radiotherapy.[23] The mean patient age was 51 years (range, 37-71 years). The rationale behind the study was that the ADSCs, which have been shown to secrete angiogenic and antiapoptotic factors and to differentiate into endothelial cells, could promote neovascularization in ischemic tissue such as irradiated tissue. Targeted areas included the supraclavicular region, the anterior chest wall after mastectomy with or without breast prosthesis, and breast after quadrantectomy. A lipoaspirate purification procedure was performed by centrifugation to remove a large part of the triglyceride portion of the tissue and disrupt the cytoplasm of the mature adipocytes to favor their rapid clearance after injection. A stromal-vascular fraction was isolated by enzymatic digestion of extracellular matrix, centrifugation and filtration, and the fractions were cultured for 2 to 3 weeks to obtain a homogenous...
cell population. To assess the presence of mesenchymal stem cells, the stromal-vascular fraction derived from the adipose tissue was cultured and characterized by flow cytometry. The number of procedures was 1 in 5 patients, 2 in 8, 3 in 6, and 6 in 1 patient. Clinical follow-up varied between 18 and 33 months (mean, 30 months). Clinical results after treatment with lipoaspirates were assessed by LENT-SOMA scoring. The 11 patients initially classified as LENT-SOMA grade 4 (irreversible functional damage) progressed to grade 0 (no symptoms), grade 1 and grade 2 in 4, 5 and 1 cases, respectively. In 1 case, no improvements were observed. In the 4 patients who had undergone mastectomy and had breast prostheses and areas of skin necrosis, the necrosis showed complete remission. In the group of 9 patients classified as LENT-SOMA grade 3, fibrosis, atrophy, and retraction progressed to grade 0 and 1 in 5 and 4 cases, respectively.

Clinical Practice Guidelines

American Society of Aesthetic Plastic Surgery and American Society of Plastic Surgeons\textsuperscript{[24]}

A joint task force of the American Society for Aesthetic Plastic Surgery (ASAPS) and the American Society of Plastic Surgeons released a position statement on the use of stem cells in aesthetic surgery during the 2011 annual meeting of ASAPS.\textsuperscript{[24]} Based on a systematic review of the peer-reviewed literature, the task force concluded that while there is potential for the future use of stem cells in aesthetic surgical procedures, the scientific evidence and other data are very limited in terms of assessing the safety or efficacy of stem cell therapies in aesthetic medicine.

Summary

Fat grafting to the breast has gained popularity with the development of improved harvesting and transplanting techniques. As an adjunct to reconstructive surgery, reported complication rates have been low, however, the clinical effectiveness, interference with screening mammography and the oncologic safety of fat grafting to the breast is still unclear. Because the impact on net health outcomes is unknown, fat grafting in reconstruction of the breast is considered investigational.

The current evidence base for the use of adipose-derived stem cells in conjunction with fat grafting to the breast has many methodological limitations and mainly report on patient and investigator satisfaction and cosmetic results. Additional research is needed for the long term effectiveness and safety of adipose-derived stem cells in conjunction with fat grafting. Therefore, the use of adipose-derived stem cells in conjunction with fat grafting to the breast is considered investigational.

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