Autologous Fat Grafting to the Breast and Adipose-derived Stem Cells

Medical Policy

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Description
Recent advances and innovations in surgical techniques and radiology and the discovery that multipotent adult stem cells are present in human adipose tissue have contributed to renewed interest in performing autologous fat grafting to the breast for aesthetic and reconstructive purposes.

Autologous fat grafting to the breast

Transplantation of autologous fat has been performed for over 100 years, primarily in cosmetic facial surgery. Since the 1980s, there has been an increased interest in autologous fat transfer for breast augmentation; however, variability in long-term results and oncologic concerns have limited its application in the breast. In 1987, the American Society of Plastic and Reconstructive Surgeons (ASPRS) Ad-Hoc Committee on New Procedures determined that fat grafting to the breast region could impede breast cancer detection because of possible complications including fat necrosis, cyst formation and calcifications, and that fat grafting to this area should be avoided. (1) This position was supported by several subsequent studies that reported severe complications due to fat grafting for breast augmentation. Until 2005, most physicians refrained from performing fat grafting to the breast. (1)

Technical advances in fat grafting such as the development of devices like liposuction cannulae and more sophisticated methods to detect breast cancer, which can provide a relatively precise distinction between microcalcifications associated with fat grafting and those associated with cancer, led physicians to develop improved fat grafting techniques. However, in 2007, the American Society of Plastic Surgeons (ASPS) and the American Society for Aesthetic Plastic Surgery (ASAPS) announced that fat grafting for breast augmentation was still not recommended based on a lack of available clinical data on the safety and efficacy of the procedure and the possibility that the procedure might interfere with cancer detection.

In 2009, the ASPS issued a new position on fat transfer, grafting, and injection to the body, which was based on a review of the literature of patients who had undergone fat grafting (238 of whom underwent fat grafting to the breast). (2) The ASPS task force concluded that fat grafting...
could be considered for breast augmentation and to correct defects associated with medical conditions and previous breast operations, although it cautioned that the results are largely dependent on technique and surgeon expertise and that because the lifetime of fat grafts is unknown, additional treatments may be necessary. Although no scientific evidence was found that specifically addressed patient selection, physicians were advised to exercise caution when considering patients at high risk for developing breast cancer (e.g. BRCA-1, BRCA-2, and/or a personal or family history of breast cancer) when determining whether a patient is an appropriate candidate for autologous fat grafting to the breast.

Adipose tissue physiology in fat grafting

Harvesting of adipose tissue by liposuction is technically easy, minimally invasive, and associated with little patient discomfort and morbidity, and small amounts (100-200 mL) can be obtained under local anesthesia.

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. There is general unpredictability and a low rate of graft survival due to partial necrosis. Other complications include oil cyst formation, indurations in either the subcutis or breast parenchyma, calcification, and severe breast deformity. (1)

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 x 10^3 stem cells, which is up to 500 times greater than the number of mesenchymal stem cells in 1 gram of bone marrow. (1) 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. (1) 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. (1)

Current methods for isolating ADSCs can involve a variety of processes which may include centrifugation and enzymatic techniques that rely on collagenase digestion followed by centrifugal separation to isolate the stem cells from primary adipocytes., Isolated ADSCs can be expanded in monolayer on standard tissue culture plastic with a basal medium containing 10% fetal bovine serum, (3) and newly developed culture conditions provide an environment within which the study of ADSCs can be done without the interference of animal serum. They also
allow rapid expansion of autologous ADSCs in culture for use in human clinical trials. A standard expansion method has not yet been established.

Yoshimura and colleagues, in an effort to address the problems of unpredictability and low rates of fat graft survival, developed a technique known as cell-assisted lipotransfer (CAL), which produces autogenous fat rich in ADSCs. (4) In CAL, half of the lipoaspirate is centrifuged to obtain a fraction of concentrated ADSCs while the other half is washed, enzymatically digested, filtered and spun down to an ADSC-rich pellet. The latter is then mixed with the former, converting a relatively ADSC-poor aspirated fat to ADSC-rich fat.

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.

**Regulatory Status**
Cytori Therapeutics, Inc. was awarded 510(k) marketing clearance in September 2006 from the U.S. Food and Drug Administration’s Center for Devices and Radiological Health (CDRH) for the Celution™ Cell Concentration System 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.

**Policy**
The use of autologous fat grafting and adipose-derived stem cells for augmentation or reconstruction of the breast is considered **investigational**.

**Policy Guidelines**
There is no specific CPT code for this procedure. One of the following CPT codes might be used:

19366: Breast reconstruction with other technique
19499: Unlisted procedure, breast

**Rationale**
This policy was originally created in 2011, with a literature search performed through May 2011. The literature on the use of fat grafting to the breast, with or without adipose-derived stem cells, consists of case series and case reports. Following is a summary of the key literature to date, detailing the largest case series using fat grafting to the breast and all identified case series using fat grafting to the breast with the supportive use of adipose-derived stem cells.

In these reports, the indications for fat grafting included augmentation, congenital breast defects, postlumpectomy or postmastectomy deformity or damaged tissue resulting from radiotherapy.
Several review articles summarize autologous fat grafting and adipose-derived stem cells. (1,3,5-7)

**Autologous fat grafting in breast augmentation and reconstruction**

In 2011, Losken and colleagues reported their experience in patients with a history of breast cancer and autologous fat grafting in secondary breast reconstruction for acquired breast deformities. (8) A retrospective review was performed for 107 patients between 1996 and 2010. The indications for fat grafting were for improvement in contour, shape, and volume of the breast following transverse rectus abdominis myocutaneous (TRAM) flap reconstruction (n =55), latissimus dorsi with or without implant (n =20), implant reconstruction (n =20), and breast conservation therapy deformity (n =12). The average volume of injection was 40 mL (range, 5-150 mL). Eighty of the 107 patients had fat injection performed only once. Patients with a history of radiation therapy had a significantly increased need for repeat fat injections. The average follow-up was 8 months (range 1 month-2.5 years). Complications occurred in 11% of patients and included fat necrosis, erythema, keloid scarring, and pain. There were 23 patients who had follow-up of greater than 6 months and were contacted for overall satisfaction with the fat injections. Seventeen patients responded, and 83% felt that the fat injections made an improvement (significant improvement n =9, moderate improvement n =5). Three patients reported no improvement.

In 2009, Illouz and colleagues reported on their experience over 25 years with 820 patients using autologous fat transplantation to the breast. (9) Patients included in the study were candidates for either breast reconstruction after tumor resection or breast augmentation and were divided into 3 groups: patients with asymmetry after mastectomy and breast reconstruction (n =381), patients with congenital breast asymmetry (n =54), and patients requesting bilateral breast augmentation (n =385). A total of 820 consecutive female patients were operated on between 1983 and 2007. Age distribution of the patients ranged from 19 to 78 years (mean 45.6 years). Twenty-five to 180 mL of fat was grafted into each breast in each session (mean 145 mL). The number of sessions needed to achieve the desired result ranged from 1 to 5 (mean 3 sessions). The total amount of fat transplanted in each breast ranged from 25 to 900 mL (mean 540 mL). Complications included ecchymosis (n =76), striae (n =36), hematomas (n =12), and infections (n =5). Long-term breast asymmetry was seen in 34 cases. Six hundred seventy patients have undergone mammography and ultrasonography 6 months and 1 year after their first intervention, and the authors state that postoperative mammograms after autologous fat transplantation identified changes one would expect after a breast reduction surgical intervention.

In 2009, Delay and colleagues reported the results of fat transplantation to the breast in 880 procedures over 10 years. (10) The lipomodeling procedures were performed for breast reconstruction (n =734), correction of congenital deformities (n =106), aesthetic breast surgery (n =30), and correction of a previous surgical defect (n=10). To compensate for fat resorption, 140 mL of fat was injected for a desired final volume of 100 mL. Clinical follow-up showed that the morphologic results with regard to the volume obtained were stable 3-4 months postoperatively if the patient’s weight remained constant. The authors stated that the postoperative radiologic appearance was that of normal breasts, sometimes showing images of fat necrosis that would not confuse the differential diagnosis of cancer for radiologists experienced in breast imaging. Oncologic follow-up at 10 years postoperatively, for the first patients treated, showed no increased risk of local recurrence of cancer or development of a new cancer. The complications included one case of infection at the harvest site, 6 cases of
infection at the injection site, and 1 case of intraoperative pneumothorax that was successfully treated in the recovery room with no further consequences. The incidence of fat necrosis was 3%.

**Autologous fat grafting and the use of adipose-derived stem cells**

In 2011, Kamakura and Ito reported on the use of autologous adipose-derived stem cell (ADSC) enriched fat grafting for breast augmentation in a prospective, nonrandomized open-label study of 20 Japanese women. (11) 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. The average number of cells per gram of harvested adipose tissue was 3.4 x 105, and mean cell viability as measured with an automated cell counting system before graft delivery was 85%. Clinical outcomes measured included improvement in circumferential breast measurement (biological response modifier [BRM]) from baseline state. There was improvement in BRM in all patients, and breast measurements were stable by 3 months after grafting. The mean BRM 9 months after had increased 3.3 cm from preoperative measurements. Through 9 months, overall patient satisfaction was 75%, and physician satisfaction 69%. The procedure was well-tolerated without any serious adverse events. Postoperative cyst formation was seen in 2 patients.

In 2008, Yoshimura and colleagues reported on the development of a novel strategy known as cell-assisted lipotransfer (CAL), in which autologous ADSCs are used in combination with lipoinjection. (4) 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.

In 2007, Rigotti and colleagues reported the results of a pilot study on the presence and effectiveness of ADSCs in 20 consecutive patients undergoing therapy for side 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). (12) (LENT-SOMA is one of the most common systems to assess the late effects of radiation therapy.) 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 liposapirate 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 five patients, 2 in eight, 3 in six, and 6 in one 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 four, five and one cases, respectively. In one case, no improvements were observed. In the four 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 five and four cases, respectively.

**National Cancer Institute’s Clinical Trial Database**

No randomized, controlled trials were identified.

There is one Phase IV interventional, non-randomized, uncontrolled trial (NCT00616135-RESTORE-2) that is post-marketing and evaluating the transplantation of autologous fat augmented with adipose-derived regenerative cells in patients with functional and cosmetic breast deformities post-segmental mastectomy, or lumpectomy. Primary outcome measures are patient and physician satisfaction with functional and cosmetic results measured as improvement in overall breast deformity at 12 months compared to baseline. Estimated enrollment is 70 with an estimated study completion date of March 2010.

**Summary**

Fat grafting to the breast for reconstructive and aesthetic purposes has been gaining popularity over the past several years, and the use of adipose-derived stem cells in conjunction with fat grafting to the breast represents a potential new advance in the field of regenerative medicine. Although there is a possible role that these stem cells could play in graft survival through both adipogenesis and angiogenesis, a complete understanding of the mechanisms of interactions among adipose stem cells and growth factors is lacking, as is the understanding of any possible role they may have in tumorigenesis. The mechanism of injected fat survival, the way to control adipose-derived stem cell differentiation and the fate of the stem cells also remains unknown. Controlled, prospective trials are needed to further investigate the many unanswered questions relating to the application of autologous fat grafting to the breast and the use of adipose-derived stem cells in conjunction with this procedure.

The impact of fat grafting and the use of adipose-derived stem cells on net health outcome in augmentation or reconstruction of the breast is unknown and therefore, is considered to be investigational.

**Practice Guidelines and Position Statements**

The American Society of Plastic Surgeons announced in 2009 that fat grafting to the breast is not a strongly recommended procedure, as there are limited scientific data on the safety and efficacy of this particular type of fat transfer. The use of adipose-derived stem cells is not addressed.

**Medicare National Coverage**

There is no national coverage determination.
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