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Review

Fat grafting for breast cancer patients: From basic science to clinical studies

R. Gennari [a,*], G. Griguolo [b,c], M.V. Dieci [b,c], V. Guarneri [b,c], B. Tavaniello [d], A. Sibilio [a], P. Conte [b,c]

[a] Department of Surgery, AuslRomagna, Ravenna, Italy
[b] Medical Oncology 2, Venetian Oncological Institute, Padova, Italy
[c] Department of Surgical, Oncological and Gastroenterological Sciences, University of Padova, Padova, Italy
[d] Department of Emergency, Plastic and Reconstructive Surgery, AuslRomagna, Cesena, Italy

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Abstract

Fat grafting in the surgical treatment of breast cancer has become popular in a short period of time because of the rising expectations of good esthetic results by the patients as well as the simplicity of the technique; however, the oncological safety for breast cancer patients remains a matter of debate. The procedure raises many questions considering that recent in-vitro studies have shown that fat grafting could promote tumor recurrence through diverse mechanisms, or even facilitate distant metastasis. We present a review of the currently available experimental and clinical data in order to describe and discuss patient selection criteria following breast cancer surgery.

Keywords: Breast cancer; Fat grafting; Lipoffiling; Oncological outcome; Safety; ASCs (adipose stem cells)

Introduction

Within the context of a multidisciplinary approach to breast cancer, the aim of surgery is the eradication of the primary tumor while offering the best possible cosmetic outcome. Breast-conserving surgery (BCS) is one of the standard options for selected cancer patients, with survival rates similar to those of patients receiving a mastectomy (MST).[1,2] In recent decades, techniques have evolved in so-called "oncoplastic breast surgery" with the aim of reconstructing defects with local tissue rearrangement.[3,4] In patients who have a reasonable tumor-to-breast size ratio, an effective local treatment, with a good preservation of esthetic outcomes, can be achieved by oncoplastic surgery. Nevertheless, large tumor size, the absence of perfect symmetry, and the effect of irradiation may create cosmetic deformities in the shape of the breast after BCS or MST.[5]

Autologous adipose tissue transfer (commonly known as fat grafting) has been demonstrated to be suitable and effective for the treatment of breast deformities and has been increasingly gaining popularity among surgeons, being used following both BCS and breast reconstructive surgery. Fat grafting (FG) – also known as lipomodeling, lipofilling and fat transfer – is a procedure used to improve the contour of the operated breast. It involves taking fat from elsewhere in the body and injecting it into the required area. The result can give a soft, natural appearance and feel, and is minimally invasive. Nevertheless its safety for breast cancer patients remains a topic for debate.

Here, we present a systematic review of available evidence from the preclinical and clinical setting regarding FG safety. On this basis, we also propose criteria for patient selection for FG following breast cancer surgery.

* Corresponding author. Department of Surgery, AuslRomagna, Viale Randi 5, 48100 Ravenna, Italy. Tel.: +39 0544 285473.
E-mail address: RGennariMD@gmail.com (R. Gennari).

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Materials and methods

Relevant literature for this review was identified by searches of MEDLINE, Current Contents, PubMed, and references from relevant articles using the search terms "lipomodeling", "lipotransfer", "fat transfer", fat grafting", "adipose augmentation", "fat transplantation", "breast cancer", "lipofilling", "autologous fat", "local recurrence", "adipose stem cells", "mesenchymal stem cells AND breast cancer", "adipocytes AND breast cancer". Papers dealing with esthetic breast reconstruction were excluded from the review. Abstracts and reports from meetings were included only when they related directly to previously published work. Only papers published in English between 2005 and March 2016 were included.

Background and history

FG of the breast has been extensively used for more than 100 years, dismantling the myth that it is a new procedure. In 1893 Gustav Neuber reported FG for the first time in plastic surgery literature. Two years later, the German surgeon Vincenz Czerny performed the first breast reconstruction by transferring a lipoma from the buttocks to the operated breast.[6] His method was also adopted by Van der Meulen a few years later. In 1910, Eugene Hollander published the first report of fat injection in the history of plastic surgery. In the mid-1950s, Peer et al. initiated scientific studies on the biology of fat graft survival. In 1987, Bircoll published his experience of breast augmentations using liposuctioned fat.[7] Unfortunately, due to the facts that his results were unimpressive and that contemporary radiographic technology was unable to differentiate calcifications due to fat necrosis from cancer lesions, his publication was followed by an unprecedented position statement from the American Society of Plastic Surgeons banning FG to the breast.[8] Stimulated by the development of liposuction, interest in free FG was reignited a few years later. A more systematic method was then advocated to address high complication rates, with technical contributions, leading to a more rigorous approach and more predictable results.

Nowadays, however, autologous fat grafting represents a promising strategy for reconstructive breast surgery. At present, the best known technique is Coleman's technique, initially published in 1995.[9,10] Briefly, fat is removed by liposuction from subcutaneous tissue, usually the abdomen or the thighs, and undergoes soft centrifugation to remove contaminants and to obtain an adipocyte-enriched specimen. Afterwards, the purified preparation is injected into the area of the breast which needs to be refilled, and therefore acts as a graft. However, reabsorption rates from 25% to 80% have been reported.[11–14] For this reason, new techniques have been proposed, based both on enzymatic treatments and on ex-vivo expansion, to enrich the lipofilling suspension in adipose-tissue-derived stem cells (ASCs) before injection with the aim of improving graft survival.[15,16]

Biological and immunological implications of lipofilling after breast cancer

Autologous fat grafting acts as more than just a filler; ASCs from adipose tissue are capable of favoring vascularization and collagen synthesis, thus enhancing skin trophicity,[17,18] a particularly interesting aspect in reconstruction after radiotherapy. However, for the same reason, safety of lipofilling techniques can be a concern when used for breast reconstruction after breast cancer.[19–25]

In fact, ASCs share many biological characteristics with bone-marrow-derived mesenchymal stem cells (MSCs), showing the same multipotency of differentiation and homing.[26–28] In addition, ASCs, like MSCs, have been shown to be capable of migrating to tumor sites.[29–31] In accordance with the increasingly recognized notion that tumor–microenvironment interaction is essential to promote cancer growth, some evidence indicates that these cells may acquire a tumor-supporting function. However, the complex and dynamic interaction between resident adipocytes, ASCs, and cancer cells has yet to be fully elucidated.

Biological effects of adipocytes on breast cancer cells

Many studies have explored the relationship between mature adipocytes and breast cancer cells. Adipose tissue is well known for its capacity to metabolize androgen to estrogen through the expression of aromatase by mature adipocytes.[25,26,30,32] Estrogen in breast tissues can reach levels 10 times greater than those in blood as a consequence of the aromatase activity of breast adipose tissue, thus enhancing growth of breast cancer cells through a paracrine mechanism.[30,32,33] There is also evidence that adipocytes surrounding breast cancer undergo, as a consequence of their interaction with breast cancer cells, significant transcriptional changes that lead to an increased expression of endocrine-related factors which in turn influence the growth of breast cancer cells through a paracrine loop.[34]

Furthermore, adipocytes produce a vast number of cytokines, also known as adipokines, which affect the biological behavior of breast cancer cells. Adipokines have also been proposed to account for the association between obesity and breast cancer.[35,36] Several of these molecules – such as matrix metalloproteinase-11, interleukin-6 (IL-6), IL-8, tumor growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), macrophage migration inhibitory factor (MIF), leptin, adiponectin and insulin-like growth factor binding protein 2 (IGFBP-2) – have been reported to be associated with a more aggressive, endocrine-resistant tumor phenotype and with the capacity for metastasis.[37–46] Promotion of epithelial mesenchymal transition (EMT) of breast cancer cells is one of the mechanisms through which this more aggressive phenotype develops. In fact, epithelial breast cancer cells undergoing EMT acquire mesenchymal