Safety of Lipofilling in Patients with Breast Cancer

Jean Yves Petit, MD[a,*], Patrick Maisonneuve, Eng[b], Nicole Rotmensz, MSc[b], Francesco Bertolini, MD, PhD[c], Krishna Bentley Clough, MD[d], Isabelle Sarfati, MD[d], Katherine Louise Gale, MD[e], Robert Douglas Macmillan, MD, PhD[f], Pierre Rey, MD[a,g], Djiazi Benyahi, MD[d], Mario Rietjens, MD[a]

KEYWORDS

• Lipofilling • Fat transfer • Breast cancer • Mastectomy • Breast conservative treatment • Breast reconstruction • Oncoplasty • Recurrences

KEY POINTS

- Biological considerations: review of experimental research and translational studies.
- Technique: differentiate the transfer technique with simple purification of the fat or an enrichment technique.
- Clinical evaluation based on a reliable statistical method to limit the risk of bias.
- Randomized trial is the best method but is not realistic in plastic surgery indications (patients refuse to submit to the surgeon choice).
- Prospective studies are more reliable than retrospective studies but require long accrual periods.
- Prospective or retrospective studies should at least be case-control studies.
- Definitive conclusions require large series, control groups with a rigorous matching of the cancer criteria, and at least 5 years' mean follow-up.

INTRODUCTION

Lipotransfer represents a technical revolution in plastic surgery and is increasingly used worldwide. Although known for several decades, it is only recently that lipofilling has found a widespread indication in patients with breast cancer to improve the results of breast reconstructions and to correct deformities after conservative treatment. Several publications in the plastic surgery literature underline the technique's versatility and the quality of the results.[1–8] They show the efficacy of lipofilling as a cosmetic procedure, and propose it as a safe, neutral biological material that is able to restore the body contour. Several studies underline the power of transferred fat to regenerate blood supply in skin disorders following radiotherapy.[9,10] Such active regeneration of tissue can be explained by the presence of a high percentage of progenitor cells included in fat tissue.[11] In this regard, attention must be drawn to the recent and abundant preclinical studies that show that adipose progenitor cells may promote breast cancer growth and metastasis. As recent studies have shown, white adipose tissue

[a] Division of Plastic and Reconstructive Surgery, European Institute of Oncology, Milan 20141, Italy; [b] Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan 20141, Italy; [c] Division of Laboratory Haematology-Oncology, European Institute of Oncology, Milan 20141, Italy; [d] Institut du Sein, Paris 75016, France; [e] Division of Oncoplastic Surgery, Waitemata DHB, Auckland, New Zealand; [f] Division of Oncoplastic Surgery, Nottingham Breast Institute, Nottingham NG51PB, UK; [g] Centro di Senologia, Genolier Swiss Medical Network, Lugano, Switzerland

* Corresponding author. Division of Plastic and Reconstructive Surgery, European Institute of Oncology, Via Ripamonti 435, Milan 20141, Italy.
E-mail address: jean.petit@ieo.it

Clin Plastic Surg 42 (2015) 339–344
http://dx.doi.org/10.1016/j.cps.2015.03.004
0094-1298/15/$ – see front matter

(WAT)–derived progenitor cells can contribute to tumor vessels, pericytes, and adipocytes, and were found to stimulate local and metastatic progression of breast cancer in several murine models.[12–14] Experimental studies provide data on the endocrine, paracrine, and autocrine activity of the transplanted fat tissue.[15] Adipocyte, preadipocyte, and progenitor cell production of adipokines and several other secretions can stimulate angiogenesis and growth of breast cancerous cells.[16] This tumor-stroma interaction can potentially induce cancer reappearance by fueling dormant breast cancer cells in the tumor bed.[17] A case report describes a local recurrence more than 13 years after apparent cure of an osteosarcoma, 1 year after lipofilling of the shoulder for cosmetic repair.[18] Moreover a case-control study revealed a significant increase of local recurrences in patients with intraepithelial breast neoplasia who underwent a lipofilling procedure for breast reconstruction.[19,20]

Concern about radiologic sequelae and surveillance difficulties by mammography caused by lipofilling has been addressed in the literature, particularly with regard to the risk of calcifications observed after lipofilling affecting the diagnosis of recurrences. This issue has largely been resolved by the distinction between suspicious fine, linear, and pleomorphic microcalcifications, and macrocalcifications related to fat necrosis as observed in most cases after fat transfer.[3,21,22]

In order to confirm the safety of lipofilling procedures in patients with breast cancer, clinical studies based on adequate statistical method and accurate follow-up are required to show that the local recurrence rate, as well as any cancer event, is not increased in fat-grafted patients with breast cancer.

BIOLOGICAL CONSIDERATIONS

There is increasing evidence that obesity, an excess accumulation of adipose tissue occurring when caloric intake exceeds energy expenditure, is associated with an increased frequency and morbidity of several types of neoplastic diseases, including postmenopausal breast cancer. Disruption of the energy homeostasis results in obesity, inflammation, and alterations of adipokine signaling that may foster initiation and progression of cancer.[23–25] Preclinical studies have suggested that differentiated cells of the WAT and WAT-resident progenitors may also promote cancer growth and metastasis. We described that CD45-CD34+ progenitors from human WAT may promote breast cancer growth and metastases in preclinical models.[13] Other recent studies, some of which are based on endogenous WAT expressing a transgenic reporter, showed a significant level of adipose cell contribution to tumor composition. However, WAT contains several distinct populations of progenitors, and these data were obtained using crude or mixed cell populations. We therefore decided to purify by sorting the 2 quantitatively most relevant populations of WAT progenitors (endothelial progenitor cells [EPCs] and adipose stromal cells) and to investigate, in vitro and in vivo, their roles in several orthotopic models of local and metastatic breast cancer. One study has recently described that EPCs are present in tissues other than the bone marrow, in particular in the adipose tissue of mice. This article reports that human WAT is a rich reservoir of CD45-CD34+ EPCs.[11] Compared with bone marrow-derived CD34+ cells mobilized in blood by granulocyte colony–stimulating factor, purified human WAT-derived CD34+ cells were found to express similar levels of stemness-related genes and significantly increased levels of angiogenesis-related genes and of fibroblast activation protein alpha (FAP-α), which is a crucial suppressor of antitumor immunity.[26] In vitro, WAT-CD34+ cells generated mature endothelial cells and endothelial tubes. In vivo, the coinjection of human WAT-CD34+ cells contributed to orthotopic tumor vascularization and significantly increased tumor growth and metastasis in models of human breast cancer in nonobese, diabetic, severe combined immunodeficient interleukin-2 receptor gamma–null mice.

LIPOFILLING TECHNIQUES

Two procedures should be differentiated according to the technique of lipofilling: the simple purification of the liposuction specimen and the enrichment of adipose tissue–derived stromal cells (ADSCs). The first, the so-called Coleman technique, does not modify the concentration of ADSCs, and the second, the so-called enrichment technique, increases the concentration of the ADSCs in the specimen that will be used for the reconstruction. In the Coleman technique[27] the fat tissue is obtained by liposuction performed on a fatty area of the body (abdomen or thighs). The specimen is purified by soft centrifugation to discard the oil and blood cells. Then the purified fat is injected in the area to be reshaped. Small differences of technique are proposed to purify the specimen without modifying the concentration of ADSCs. The main drawback of this technique is the frequency of reabsorption of the fat tissue injected in the following 6 months.[28,29] In contrast, the enrichment technique divides the specimen obtained by liposuction into 2 parts. The first part is reserved for the final injection. The second is processed in a machine using an