Oncological Safety of Autologous Fat Grafting after Breast Conservative Treatment: A Prospective Evaluation

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Abstract: Autologous fat graft to the breast is a useful tool to correct defects after breast conservative treatment (BCT). Although this procedure gains popularity, little is known about the interaction between the fat graft and the prior oncological environment. Evidences of safety of this procedure in healthy breast and after post-mastectomy reconstruction exist. However, there is paucity of data among patients who underwent BCT which are hypothetically under a higher risk of local recurrence (LR). Fifty-nine patients, with prior BCT, underwent 75 autologous fat graft procedures using the Coleman’s technique, between October 2005 and July 2008. Follow-up was made by clinical and radiologic examination at least once, after 6 months of the procedure. Mean age was 50 ± 8.5 years, and mean follow-up was 34.4 ± 15.3 months. Mean time from oncological surgery to the first fat grafting procedure was 76.6 ± 30.9 months. Most of patients were at initial stage 0 (11.8%), I (33.8%), or IIA (23.7%). Immediate complication was observed in three cases (4%). Only three cases of true LR (4%) associated with the procedure were observed during the follow-up. Abnormal breast images were present in 20% of the postoperative mammograms, and in 8% of the cases, biopsy was warranted. Autologous fat graft is a safe procedure to correct breast defects after BCT, with low postoperative complications. Although it was not associated with increased risk of LR in the group of patients studied, prospective trials are needed to certify that it does not interfere in patient’s oncological prognosis.

Key Words: adipocyte stem cell, autologous fat graft, breast cancer, breast reconstruction, local recurrence

Breast conservative treatment (BCT) is a standard of care for early breast cancer. As definition, BCT intends to give local treatment as effective as mastectomy, but with better cosmetic results once the breast tissue is spared (1,2). As the publications of the Milan I Trial and the NSABP-06 Trial, increasing numbers of women sought BCS (3–5). Rates of BCS vary from 10% to 67% in different U.S centers (6–9). Despite the high quote of patient’s satisfaction on these studies (75–96%), severe asymmetry is noted in almost 30% of then (10).

Correction of breast asymmetry after BCT may be very challenging, especially in type 2 and 3 cosmetic sequelae as described by Clough et al. (11). It is in this scenario that autologous fat graft seems to be a good alternative to fill the defects and improve cosmetic outcome of BCS (12–14). Despite the discussion about the technique used and predictability of results, the main concern among surgeons is on its safety regarding the oncological aspects, especially in those who underwent BCT (12,15–17).

Medical societies throughout the world expressed the concern about surgeons performing this procedure without clear evidence of its safety (18,19). In 2009, de American Society of Plastic Surgery set up a task force to assess the indications, safety and efficacy of autologous fat transfer (18). The conclusion of this task force was that most of what is known comes
from case series and expert’s opinion, which means a low grade of scientific evidence. However, the task force did not find any association between breast fat graft and local recurrence (LR), so they were not able to give further recommendations addressing this issue than considering this experimental in patients with breast cancer and that prospective controlled studies should be performed.

Hypothetically, the transfer of adipose-derived stem cells (ADSC) or adipose-derived mesenchymal stem cell (ADMSC) could induce silent tumor cells to reproduce and predispose to LR. “In vitro” and animal models basic researches are conflictive and show positive and also negative association with breast cancer cell proliferation (20–24).

On the other hand, case series did not demonstrate an association between autologous fat graft and breast cancer recurrence, including large individuals’ series and multi-institutional studies (25–27). However, most of these series focused on fat grafting after mastectomy and reconstruction, and few cases are dedicated to study its impact on BCT patients.

Local recurrence is more frequent in patients with BCT compared with mastectomy, without impact on mortality (1–4). This fact maybe due to the existence of dormant tumor cells in the breast parenchyma (24,28). Therefore, if autologous fat graft can stimulate those dormant tumor cells, it should happen indeed more frequently in patients treated with breast conservation rather than mastectomy. However, this information lacks in many studies.

It is in this scenario of lack of strong scientific evidence that we present a prospective evaluation of 59 patients with prior BCT undergoing 75 autologous breast fat graft procedure and analyze the oncological results along time, focusing in procedure safety, local control and disease-free survival.

MATERIALS AND METHODS

Patient’s Selection

From October 2005 to July 2008, we prospectively evaluated 59 patients that underwent 75 breast fat grafting procedures at the European Institute of Oncology (Milan, Italy). All patients had been submitted to a previous BCT for oncological reasons, which lead to an aesthetical breast defect. All patients were visited by a single surgeon who indicated the procedure. Only patients free of breast locoregional disease were considered eligible to the procedure after an accurate breast clinical and instrumental evaluation. The presence of stable bone metastasis was not an exclusion criteria.

Preoperative Evaluation

All patients scheduled for the fat-grafting procedure were evaluated preoperatively with clinical and breast image exams. Bilateral mammogram and breast ultrasound (U.S.) were requested for all patients. After explanation of the procedure and the signature of an informed consent, all patients agreed to undergo the surgery. Preoperative pictures were taken in all cases, and the breast defect was measured by a centimeter on its two major axis, and finally on its depth by an approximate measurement. If there were one or more defects, they were measured and documented as defect 1, 2, 3, and so on.

Surgical Technique

The procedure was performed under local or general anesthesia, depending on the patient’s clinical conditions and risks. Local anesthesia was preferable, and general anesthesia was recommended in cases that there was a need of harvesting a great amount of fat tissue, when an associated procedure was indicated (prosthesis exchange and capsulotomy, for instance), or when the patient showed extreme anxiety.

The whole procedure of fat harvesting and grafting was performed according to the Coleman’s technique (12) with minimal modifications.

Follow-Up

Follow-up was made at the outpatient’s clinics, at least once after 6 months of the procedure. It consisted of clinical evaluation. Mammogram was requested every year associated with breast ultrasound when needed. When patient could not be reached, telephone contact was made.

Statistical Analysis

Progression-free survival curve was estimated by the Kaplan–Meyer method with significance level of 5%. Time between the fat grafting and last follow-up was studied by mean time and median. The software used was SAS, version 9.2 (SAS Institute, Cary, NC).
RESULTS

Mean age of the women at the time of fat grafting was 50 ± 8.5 years, and mean follow-up was 34.4 ± 15.3 months, and more than 75% of them had follow-up greater than 45.9 months. Procedure was conducted under local anesthesia in 58 cases (77.3%) and under general anesthesia in 17 cases (22.7%). Ninety-eight percent of the defects were localized exclusively in the breast parenchyma, and just in one patient, defect was also present in the axilla. Right and left breast were equally affected (50.7 vs. 48%, respectively). Population’s characteristics by patient and by procedure are described in Table 1.

Only five patients had more than one defect in the breast, and two of them had three defects. Mean volume of fat preparation injected was 52.3 ± 28.7cc. Second and third defects had a mean volume injected of 32.8cc and 52.8cc, respectively. In 78.7% of the cases, fat was harvested from the abdomen and in 10.7% from the hips, in the other cases association between hips, abdomen, and knees were made.

Immediate complication was observed in three cases (4%) and consisted of fat necrosis in two patients and cellulites in one patient. All cases were managed clinically with no further complications.

Follow-up occurred at least once 6 months after the procedure. In 15 cases (20%), the mammogram was normal before the procedure and exhibited abnormalities afterwards. Lesions were considered suspicious in six cases, and breast biopsy was performed. In two cases, biopsies resulted positive and in four cases negative (Table 2). In eight cases, (10.6%) postoperative breast images were missing.

Most of patients were at initial stage 0 (11.8%), I (33.8%), or II A (23.7%; Fig. 1). Thirty-five patients (59.3%) had undergone quadrantectomy with axillary dissection (QUART), and 14 patients (23.7%) underwent quadrantectomy with sentinel node biopsy (SNB). Only 10 patients (16.9%) underwent quadrantectomy alone. Oncoplastic techniques were used in just nine patients (15.3%). External radiotherapy was present in 56 patients (94.9%).

During the follow-up, there were four cases of ipsilateral breast recurrence. However, in one case, LR was suspected in the day of the procedure and was confirmed by histology 1 week after it. Therefore, we do not associate this to the fat grafting procedure. All three LR were invasive ductal carcinoma and were considered true LR once they happened in the same quadrant of the primary tumor. Characteristics of the primary tumor are compared with its recurrence in Table 3.

Mean time from oncological surgery to the first fat grafting procedure was 76.6 ± 30.9 months. Considering that we found just three cases of true LR (4%)
in 34 months of follow-up, this would produce a rate of 1.4% LR per year. The progression-free survival from time of fat grafting to LR is shown in Figure 2.

**DISCUSSION**

Autologous fat graft is a valuable and promising tool to help breast and plastic surgeons to correct defects after BCT. Procedure is simple and can be performed mostly under local anesthesia, which means no hospital stay and low cost. Complication’s rate was about 4% and was of simple management. Many papers confirm this low rate of postoperative complications, which makes autologous fat graft to be a popular choice for surgeons and patients (29–31).

Unfortunately, efficacy of the procedure is not predictable. Despite of our experience and others from the literature (25–27,29–33), it is still very difficult to predict whether the fat graft will attach or not. In this study, only in 16.8% of the cases a further fat graft procedure was performed. This could means that a good result was achieved in most of the cases. However, those numbers are underestimated, once in the follow-up, there are patients already scheduled to a new procedure or others who still show the breast defect but do not want to undergo another procedure. The lack of an objective evaluation of the efficacy is a weak point of his paper, as it is in review articles, which shows a difficulty in assessing its efficacy (18,31,33,34).

A great concern of our study was about the abnormal radiologic features that fat graft could produce in the breast. Although some evidences in literature shows that breast fat graft is not correlated with fea-

![Figure 1. Distribution of pathological breast cancer stage of the 59 patients.](image1)

![Figure 2. Progression-free survival from fat grafting procedure.](image2)

**Table 3. Characteristics of the Primary Tumor and the Local Recurrence after Fat Graft Procedure**

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<tr>
<th>Patient</th>
<th>Primary tumor</th>
<th>Recurrence</th>
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<tr>
<td></td>
<td>Location</td>
<td>Histology</td>
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<tr>
<td>1</td>
<td>SIQ</td>
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tures that could mask hidden lesions or increase the number of unnecessary biopsies (13,14,16,17,34–36), this was a critical argument to be evaluated. Actually, we found no significant increase in abnormal breast images after the procedure (20%) if we compared with other types of breast intervention such as reduction mammoplasty, which can produce up to 85% of postoperative radiologic features (37–39). Most abnormal breast images associated with fat graft are macrocalcification and oil’s cyst that are easily recognized as benign lesions by trained radiologists (39,40).

From six cases warranting biopsies in our study, only two irregular nodules resulted in LR. Little information exists on LR following autologous fat graft after BCT; therefore, there is no specific radiologic pattern of it. Based on our observation, we suggest that suspicious nodular lesions after autologous fat graft should be biopsied to rule out LR. However, it is evident that all suspicious lesions should be biopsied.

Local recurrence was the main goal of this study. Although the use of autologous fat graft is rising in clinical practice, the real oncological impact on patients who have had breast cancer is still unknown (28–31,33,34,41–44). Delay et al. (25) published data on 10 years follow-up of more than 880 fat grafting procedures, including 42 cases after BCT and found no increased rate of LR. Illouz et al. (32) in his personal experience with 820 patients undergoing breast fat grafting found no LR at all in the group of 30 patients with previous BCT. Two recent systematic reviews addressed the oncological issue and found no clinical evidence of increased LR in any study, although they consider that safety should be objective of prospective and controlled studies (31,34).

In our study, LR was observed only in three cases out of 75 procedures (4%), and all of them happened in the same quadrant of the primary tumor; therefore, they can be considered true LR and not a “new tumor.” It is acceptable in the literature that LR occurs in the rate of 1–1.5% per year (1–4). In this series, the mean time between oncologic surgery to fat graft was 76 months, and mean follow-up time was 34 months. So, 4% of LR in 34 months produces a rate of 1.4% LR per year, which seems acceptable for BCT. Moreover, timing of recurrence was very different in the three cases (Fig. 2), showing that there is no pattern of LR, linking these facts much more to a chance rather than to the fat grafting procedure.

Patient’s selection and the absence of a control group to match the results can be considered a bias to this study. The majority of patients in the study were patients of good oncological prognosis presenting with initial breast cancer pathological stages (0, I, and IIA), evidencing a selection for LR low-risk patients.

Recently, Petit et al. (45) published data about autologous fat transfer in previous breast cancer patients treated with mastectomy or BCT and matched the follow-up with a control group. There was no difference in LR in patients with previous invasive carcinoma. However, LR in patients with previous ductal carcinoma in situ (DCIS) was significantly higher. Difference between mastectomy and BCT group was not of statistical significance. Despite of the findings, the authors conclude that breast lipofilling seems to be safe, but this higher incidence of LR in the DCIS group must be better studied once it can be biased by many factors, including the design of the study.

The fact is that the role of ADSC in a previous cancerous environment is still unknown. Bench basic research shows conflicting results about the interaction between ADSC with breast tissues and cancer cells. There is data that suggest ADSC promoting or causing breast cancer in “in vitro” and animal models (46–48). Mechanisms of this interaction may be multiple, including liberation of adiponectin and leptin from ADSC promoting cellular proliferation, increase in the peripheral aromatization and liberation of angiogenic factors such as vascular endothelial growth factor (20,21,23,24,47). This could theoretically induce the awakening of a dormant tumor cell or even interfere with adjuvant hormonal therapies.

Moreover, Pearl et al. (49) published a recent review on stem cell biology and its behavior in the breast environment. It seems that ADMSC interacts with adjacent stroma and potentially promotes proliferation of fibroblasts and other cell lines promoting LR, as occurs in prostate cancer with the “fibroblast-associated carcinoma” (49,50). Recently, a case report of a osteosarcoma treated, with a history of surgery and chemotherapy were carried out 13 years before, has been published, and after 18 months of a autologous fat graft to correct the surgical defect, a LR happened (51). The authors discuss the interaction between ADSC and the LR as this pattern of late recurrence is extremely rare.

In contrast, there are some studies that show ADSC inhibiting tumor growth and metastasis of breast cancer in animal models (22,24,52). Therefore, the exact role and intrinsic interaction between ADSC, normal
breast and breast cancer cell and its environment must be further investigated.

CONCLUSION

Autologous fat graft is a promising tool to correct defects after BCT. Procedure is simple and is associated with low rates of postoperative complications. LR rate was not higher than the expected for this low-risk group of patients. The role of ADSC in previous cancer environment is still unclear. Further investigation is needed, although prospective randomized trials will be difficult to be carried out because there is not another technique or “filler” that can substitute the role of fat grafting in correcting breast defects. Data should be collected and gathered from multicenter institution to enlarge the evidence of the safety of fat grafting after BCT.

CONFLICTS OF INTEREST

The authors declare no conflicts of interests or sponsorships, grants, and patents. Study was approved by the ethics committee, and all patients were given an informed consent.

REFERENCES


