Locoregional recurrence risk after lipofilling in breast cancer patients

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Background: Lipofilling has been indicated for postmastectomy and postlumpectomy breast reconstruction. The clinical literatures underline its technical efficacy but experimental studies raise important questions about the potential detrimental effect of adipocytes on the stimulation of cancer growth and reappearance.

Design: We collected 321 consecutive patients operated for a primary breast cancer between 1997 and 2008 who subsequently underwent lipofilling for reconstructive purpose. For each patient, we selected two matched patients with similar characteristics who did not undergo a lipofilling.

Results: Eighty-nine percent of the tumors were invasive. Median follow-up was 56 months from the primary surgery and 26 months from the lipofilling. Eight and 19 patients had a local event in the lipofilling and control group, respectively, leading to comparable cumulative incidence curves [P = 0.792; Hazard Ratio Lip vs No Lip = 1.11 (95% confidence interval 0.47–2.64)]. These results were confirmed when patients undergoing quadrantectomy and mastectomy were analyzed separately and when the analysis was limited to invasive tumors. Based on 37 cases, the lipofilling group resulted at higher risk of local events when the analysis was limited to intraepithelial neoplasia.

Conclusions: Lipofilling seems to be a safe procedure in breast cancer patients. Longer follow-up and further experiences from oncological series are urgently required to confirm these findings.

Key words: breast cancer, breast reconstruction, fat grafting, lipofilling, lipotransfer, recurrence

introduction

The lipofilling technique has been used since many years in aesthetic surgery. More and more frequently lipofilling is proposed to improve the results of the total or partial reconstruction in breast cancer patients [1–5]. Although several teams published results of total breast reconstruction with repeated sessions of lipofilling, for most authors, the technique remains indicated for local improvement of small defects or asymmetry only [6–8]. The simplicity of the technique as well as the absence of visible scar explains the great interest of the
plastic surgeons and the rapid shift of lipofilling indications to breast cancer patients. Most studies published in the literature focus on technique, complications, fat graft survival and cosmetic results. While they are mainly dealing with the risk of microcalcifications observed on the radiological imaging during the follow-up, only a few studies focused on cancer recurrences after lipofilling [4, 9, 10]. But we know from experimental studies that adipocytes and white adipose tissue-resident progenitors are able to produce different growth factors, which could act on cancer cells through a paracrine activity [11–18]. It is therefore mandatory to raise the question of recurrence risk for patients undergoing a lipofilling in the area of the previous breast cancer treatment particularly after conservative treatment.

The review article by Lohsiriwat et al. [19], on experimental studies found that adipocyte, preadipocyte and progenitor cell secretions can stimulate angiogenesis and cell growth. He also underlined that the ‘tumor–stroma interaction’ can potentially induce cancer reappearance by ‘fueling’ dormant breast cancer cells in tumor bed. However, there is lack of translational research that proves this concern in clinical aspect. No study on the effects of lipotransfer on human cancer breast cells in vivo is available. The direct and indirect effects of lipotransfer in breast cancer patient, highlighting pro and con related issues remain unclear. Today, no informed consent can be given to our patients stating that lipofilling does not stimulate fueling of dormant cancer cells or eventually induce new cancer cells [20].

In 2007, the French Society of Plastic Surgery addressed the question of cancer safety after lipofilling in breast cancer patients. The Society sent a recommendation to the French plastic surgeons to postpone the lipofilling in the breast with or without breast cancer history unless it is carried out under prospective controlled protocol [21]. In 2009, the American Society of Plastic Surgeons (ASPS) set up a task force (ASPS Fat Graft Task Force) to assess the indications, the safety and efficacy of autologous fat grafting [4]. The ASPS task force stated that the question of cancer risk in the literature is based on a limited number of studies with few cases, no control group, made on expert opinion, or case reports. Although no evidence of increase in cancer recurrence risk due to lipofilling has been observed or published, they cannot give definitive recommendations in what concerns the cancer risk. The purpose of our study was to analyze the oncologic outcome of a series of 321 lipofilling procedures at the European Institute of Oncology (IEO) during the past 5 years and to compare these results with those of a control group of patients with similar characteristics who did not underwent the procedure.

what is fat grafting surgical procedure?

At present, the technique used by the majority of surgeons was published in 1995 by Coleman [22]. Aspirated fat tissue is taken, centrifuged and injected in the area where a filling is necessary. The fat is removed by liposuction from the subcutaneous tissue, usually from the abdomen or from other donor sites according to the morphology of the patient. The specimen is subjected to soft centrifugation to remove blood cell contaminants and obtain an adipocyte-enriched preparation. Recently, a number of new techniques have been described, mostly based on enzymic treatments, to increase the percentage of preadipocyte in the specimen allowing a possible better take of the graft [23–26]. Fat injection into the breast could result in fat necrosis, cyst formation and indurations that could be mistaken as cancerous calcifications. Moreover, the degree of reabsorption of the injected adipose tissue is unpredictable. Rigotti et al. [27] demonstrated that lipofilling is more than just a filler: it also enhances skin trophicity, which is interesting after radiotherapy.

methods

study population

We selected, from the IEO Breast Cancer Database, all the women operated between 1997 and 2008 for primary breast cancer at the IEO. We then identified all the patients who subsequently underwent a lipofilling procedure for reconstructive purpose at our institute, with no tumor recurrence between the primary and the lipofilling intervention. We excluded women with synchronous distant metastases at diagnosis, bilateral or recurrent tumor, previous cancer and those receiving neoadjuvant treatment. A total of 321 patients were finally included in the current study.

For each of the 321 patients in the study group, we selected from the same database two control patients who underwent surgery for a primary breast cancer at the IEO but did not undergo a lipofilling procedure. To ensure homogeneity between the study group and the control group, each matched control was randomly selected from a list of potential controls who had the same characteristics as the corresponding study patient, namely the same age (within 5 years), year of surgery (within 2 years), type of surgery (quadrantectomy versus mastectomy), histology [invasive cancer versus ductal intraepithelial neoplasia (DEN) versus lobular intraepithelial neoplasia (LIN)], pathological tumor size (1 versus 2 versus 3) and estrogen receptor status (negative versus positive). Also, as shown in Figure 1, a control patient had a disease-free follow-up time at least as long as the time window between tumor primary surgery and lipofilling procedure of the corresponding case patient.

Data on patient medical history, type of surgery, pathologic assessment of morphologic and biologic features were retrieved from the IEO Breast Cancer Database. As for the follow-up information, in case of unavailability of a clinical examination during the previous 6 months, the patients were contacted by telephone. When the patient was not available, survival status was ascertained by the registry office.

statistical methods

The chi-square test was used to assess differences between the study and the control group in the distribution of prognostic variables. The main end point was the cumulative incidence of local event. Any event involving a local reappearance, such as local relapse or locoregional relapse or local

![Figure 1. Matched cohort study design.](https://academic.oup.com/annonc/article-abstract/23/3/582/224923)
relapse with synchronous metastases, was counted as local event. Any other type of event was counted as a competing event. In case of no events, the observation was censored at the last follow-up visit. The cumulative incidence of local events was computed in a competing risk framework and compared across different subgroups by means of the Gray test. The prognostic impact of the lipofilling on the risk of local events was evaluated using the univariate Cox proportional hazard regression model and expressed as hazard ratio (HR) with 95% confidence intervals (CIs).

All analyses were carried out with the SAS software (SAS Institute, Cary, NC) and the R software (The R Development Core Team 2004; Free Software Foundation, Boston, MA). Tests were two-sided.

## Results

Patients’ characteristics are presented in Table 1. Median age was 45 years (range 22–71) in the lipofilling group and 46 years (range 26–69) in the controls. Eighty-nine percent of the tumors were invasive, with a median diameter size of 1.6 cm in the lipofilling group and 1.7 cm in controls. The majority of tumors were operated with a mastectomy (61%) and resulted in a node-negative disease (59% in the lipofilling group and 57% in controls). Median time from oncologic surgery to lipofilling was 26 months (range 2–128). No relevant difference in the distribution of the characteristics was observed.

Table 2 describes follow-up and events. Overall, median follow-up was 56 months from primary surgery (ranges from 8 to 155 months) and 26 months from baseline (ranges from 1 to 128 months). Eight and 19 patients had a local event in the lipofilling and control group, respectively, this leading to comparable cumulative incidence curves [Gray test $P$ value = 0.792; HR$\text{Lipo vs No lipo} = 1.11$ (95% CI 0.47–2.64); Figure 2]. These results were confirmed even when the two groups of...
patients who underwent breast conservative treatment (BCT) and mastectomy were analyzed separately (Figure 3A and B). Again, no significant difference was observed in patients with invasive cancers (Figure 3C). On the contrary, the lipofilling group resulted at higher risk of local events (three events) compared with the control group (no event) when the analysis was limited to DIN and LIN (Gray test \( P < 0.001 \); Figure 3D).

The position of the scar is not always at the exact primary tumor site. Neither the lipofilling site nor the scar position is always in the same location as shown in Table 3. However, majority of the recurrence sites were close to the lipofilling sites (11 of 13 cases excepted case number 11 and 13).

Since the patients in the lipofilling group underwent a complete clinical examination and were declared disease free at the time of the lipofilling, they were less likely to have a local recurrence in the first months of observation compared with the patients in the control group, who were not necessary visited in close proximity to the baseline. So, in a sensitivity analysis, we set a ‘wash-out’ period of 6 months after the baseline to get rid of the potential prevalent events of the control group and obtained a not significant difference in cumulative incidence of local events overall [Gray test \( P = 0.179 \) and HR Lip vs No lipo = 1.71 (95% CI 0.67–4.39)].

### Discussion

To reach a reliable conclusion on cancer safety of lipofilling in breast cancer patients, we set up a retrospective comparison between our 321 lipofillings and 642 matched patients with similar characteristics who did not undergo a lipofilling procedure. Our results confirm the absence of significant difference between the two groups when comparing the local events. These results were confirmed when patients undergoing quadrantectomy and mastectomy were analyzed separately and when the analysis was limited to invasive tumors. Notably, when limiting the analysis to the 37 patients with intraepithelial neoplasia, the lipofilling group resulted at higher risk of local events (four events) compared with the control group (no event).

When looking at the local recurrences occurring in the DIN and LIN group, three occurred after mastectomy and one after BCT. In all four cases, the margins after primary surgery were free of disease. Such statistical difference should be questioned before concluding for an increasing risk of locoregional recurrences after lipofilling. According to the review literatures, the rate of locoregional recurrences for DIN and LIN group is 1.5% per year and should correspond to a median rate of 2% in our series after 26-month median follow-up [28, 29]. However, we found no event in the control group; such difference in our control group could be considered as a sample error.

Intraductal proliferative lesions of the breast have traditionally been divided into three categories: usual ductal hyperplasia, atypical ductal hyperplasia and ductal carcinoma in situ (DCIS). It should be noted, however, that the term ‘DCIS’ encompasses a highly heterogeneous group of lesions that differ with regard to their mode of presentation, histopathological features, biological markers and risk for progression to invasive cancer.

### Table 2. Summary of all events

<table>
<thead>
<tr>
<th>First event</th>
<th>Invasive Lipofilling no. 284</th>
<th>Invasive Controls no. 568</th>
<th>In situ Lipofilling no. 37</th>
<th>In situ Controls no. 74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local invasivea</td>
<td>1</td>
<td>11</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Local and regionalb</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Local and distantc</td>
<td>2</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Regionalb</td>
<td>5</td>
<td>9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Distant</td>
<td>13</td>
<td>27</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Deaths as first event</td>
<td>–</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total first events</td>
<td>22</td>
<td>54</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Total deaths</td>
<td>2</td>
<td>13</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median follow-up from surgery (months)</td>
<td>56</td>
<td>57</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Median follow-up from baseline (months)</td>
<td>25</td>
<td>26</td>
<td>24</td>
<td>29</td>
</tr>
</tbody>
</table>

*Treated as ‘Local event’ in the following analyses.

bEleven axillary recurrences, 1 supraclavicular, 1 subclavicular and 1 in the internal mammary chain.
In our analysis, we define DIN as a proliferation of malignant epithelial cells within the breast parenchymal structures with no evidence of invasion across the basement membrane [1]. This lack of invasive foci may be confirmed with immunohistochemical assessment for the presence of myoepithelial cell (e.g. smooth muscle actin, smooth muscle myosin) or basement membrane (type IV collagen, laminin) [30].

Figure 3. Cumulative incidence of local events: (A) after conservative surgery, (B) after mastectomy, (C) in patients with invasive cancer and (D) in patients with DIN+LIN cancer. *Local, locoregional, local and distant. **HR Lipos vs No Lipos not calculable. CI, confidence interval.

Table 3. Location of scar, lipofilling, recurrence and Primary tumor sites in 13 cases with local recurrence

<table>
<thead>
<tr>
<th>Scar position</th>
<th>Lipofilling location</th>
<th>Recurrence</th>
<th>Primary tumor site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Radial IE</td>
<td>QS</td>
<td>QSE</td>
</tr>
<tr>
<td>2</td>
<td>Racket SE</td>
<td>QS</td>
<td>QSE</td>
</tr>
<tr>
<td>3</td>
<td>Radial SE</td>
<td>Periareolar</td>
<td>QSE</td>
</tr>
<tr>
<td>4</td>
<td>Racket IIn</td>
<td>Parasternal</td>
<td>QIIn</td>
</tr>
<tr>
<td>5</td>
<td>Racket SE</td>
<td>QSE + QIIn</td>
<td>QSE</td>
</tr>
<tr>
<td>6</td>
<td>Racket SE</td>
<td>QISn</td>
<td>QS</td>
</tr>
<tr>
<td>7</td>
<td>Radial SE</td>
<td>QSE + retroareolar</td>
<td>QSE</td>
</tr>
<tr>
<td>8</td>
<td>Superior circumareolar</td>
<td>QS</td>
<td>QSE</td>
</tr>
<tr>
<td>9</td>
<td>Racket SE</td>
<td>QSE</td>
<td>Axilla region</td>
</tr>
<tr>
<td>10</td>
<td>Racket SE</td>
<td>QSE + axilla</td>
<td>Axilla region</td>
</tr>
<tr>
<td>11</td>
<td>Radial SE</td>
<td>QIE</td>
<td>Axilla region</td>
</tr>
<tr>
<td>12</td>
<td>Superior circumareolar</td>
<td>QSE</td>
<td>Axilla region</td>
</tr>
<tr>
<td>13</td>
<td>Radial E</td>
<td>QS</td>
<td>Sternal region</td>
</tr>
</tbody>
</table>

Q, quadrant; S, superior; I, inferior; E, external; In, internal; C, central.
With regards to other studies on the topic, a questionable methodology has been used by Rigotti et al. [31] to prove the safety of lipofilling in breast cancer patients. The time interval between the radical mastectomy and the first fat grafting session (Period I) was used as the control for the time after the first grafting session (Period II). It has been demonstrated that the majority of local relapses after mastectomy occurs within 5 years and reach a plateau phrase after >5 years [32–34]. In the series presented, the median follow-up of Period I is exactly 23 months, corresponding to the time interval when the majority of relapses occur. Therefore, it is expected that the incidence of local recurrences is higher in Period I independently from fat grafting and although the equivalent patient population the two periods are not comparable.

With regard to the mentioned series, we wonder why the 104 patients treated with conservative surgery for breast cancer have been excluded from patient population, including only those who had a modified radical mastectomy. After conservative surgery, the remaining glandular tissue after tumor removal is at higher risk of relapse if compared with the skin and the thoracic wall after a modified radical mastectomy. Moreover, it has been demonstrated that ~85% of breast relapses after conserving surgery are confined to the same quadrant of the breast as the primary tumor [35]. Fat grafting is used to correct postquadrantectomy defects; therefore, patients who underwent conservative surgery and requiring defect correction are the best candidates to understand the interaction between fat grafting and breast tissue.

Another clinical series by Illozu et al. [36] reviewed a personal series of 820 patients with lipofilling, and only 381 patients were cancer patients; other indications were for congenital breast asymmetry and cosmetic augmentation without cancer history. However, they could not make the conclusion in term on oncological safety because 40% of the patients were lacking of oncological data and follow-up.

Rietjens et al. reported clinical series focused on lipofilling in breast cancer treatment and reconstruction. They followed 158 patients and found that postoperative complication rates are very low and there is little alteration in follow-up mammograms. Despite they found only one recurrence in 18-month follow-up period and this recurrence probably occurred before lipofilling. They concluded that the potential risk of local ‘dormant’ tumor cells being stimulated to induce a local recurrence is still unclear [5]. Another series of 880 lipofilling procedures by Delay et al. [3] demonstrated a low complication rate and positive results. He also suggested that pre and postoperative examination by a radiologist specialized in breast imaging is necessary to limit the risk that a cancer may occur coincidentally with lipofilling.

In 2008, Chan et al. [37] reviewed eight studies on autologous fat transfer with a focus on breast cancer surgery. In such review, most indications of lipofilling were not for breast cancer patients but for benign purpose. No specific oncologic follow-up was mentioned.

The same concern of stimulatory effect of lipofilling method is also found in other type of solid tumor. Recently, Perrot et al. [38] reported a case of a late local osteosarcoma recurrence occurred 13 years after primary tumor treatment and several months after lipofilling. They underlined the uncommon late recurrence in this type of tumor; as a result, they investigated the relationship of osteosarcoma tumor growth with fat injections in preclinical models. They observed that the adipocyte or progenitor cells promoted osteosarcoma tumor growth.

Some limitations of our study are hereafter discussed. Firstly, to prove the safety of the lipofilling in breast cancer patients, a randomized trial would have been required. It is true though that a randomization could only be proposed if there is an alternative procedure to the lipofilling such as the injection of tissue fillers. However, the surgical complication of these fillers seems too high to propose such randomized study and there is no oncological safety in these products available [39, 40]. Secondly, since the patients in the lipofilling group underwent a complete clinical examination and were declared disease free at the time of the lipofilling, they were less likely to have a local recurrence in the first months of observation compared with the patients in the control group, who were not necessary visited in close proximity to the baseline. This could have lead to a biased comparison between cases and controls. We tried to overcome this problem by setting a ‘wash-out’ period of 6 months after the baseline to get rid of the potential prevalent events of the control group and presented the results in an additional sensitivity analysis.

**conclusion**

According to these preliminary results, lipofilling seems to be a safe procedure in breast cancer patients. Longer follow-up and other experiences from oncological series are urgently required to confirm these findings.

**disclosure**

The authors declare no conflict of interest.

**references**