Fat Grafting after Invasive Breast Cancer: A Matched Case-Control Study

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Background: Fat grafting has been widely indicated for postmastectomy and postlumpectomy breast reconstruction. The literature emphasizes the clinical efficacy of fat grafting, but experimental studies raise important questions about the recurrence risk because of the stimulation of remaining cancer cells by progenitor or adult adipocytes. Because breast conservative treatment provides a higher risk of residual cancer cells in the breast tissue compared with mastectomy, the authors set up a matched case-control study of fat grafting versus no fat grafting after breast conservative treatment.
Methods: The authors collected data from 322 consecutive patients operated on for a primary invasive breast cancer who subsequently underwent fat grafting for breast reshaping from 2006 to 2013. All patients were free of recurrence before fat grafting. For each patient, the authors selected one patient with similar characteristics who did not undergo fat grafting.
Results: After a mean follow-up of 4.6 years (range, 0.1 to 10.2 years) after fat grafting, or a corresponding time for controls, the authors observed no difference in the incidence of local events (fat grafting, $n = 14$; controls, $n = 16$; $p = 0.49$), axillary nodes metastasis (fat grafting, $n = 3$; controls, $n = 6$; $p = 0.23$), distant metastases (fat grafting, $n = 14$; controls, $n = 15$; $p = 0.67$), or contralateral breast cancer (fat grafting, $n = 4$; controls, $n = 4$; $p = 0.51$).
Conclusion: Fat grafting seems to be a safe procedure after breast conservative treatment for breast cancer patients. (*Plast. Reconstr. Surg.* 139: 1292, 2017.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Fat grafting has been carried out in aesthetic surgery worldwide for many years. More recently, in breast cancer patients, thousands of fat grafting procedures have been performed to complete or improve the results of partial or total breast reconstruction. Clinical studies have been published to demonstrate the reliability of this procedure to improve the morphologic results of the breast reconstruction.[1–7] The cancer safety of fat grafting in breast cancer patients has also been emphasized in several publications. However, the small number of patients included in the series, the short follow-up, and the lack of a control group cannot be totally reassuring in light of the experimental studies showing the role of adipose tissue in the stimulation of dormant cancer cells after breast conservative treatment or mastectomy.[8–10] White adipose tissue-resident progenitors are able to produce different proteins (leptin) that could act on cancer cells through paracrine and systemic activity. More than 30 publications in basic science journals stress the role of fat tissue in the stimulation of cancer through paracrine activity and also, according to several authors, through systemic stimulation.[11–14] There is also the question about possible bias introduced in the experimental studies, such as the use of pure fat stem cells, which is not the case in clinical application in humans. It can also be stressed that biological modifications of nude mice introduce another source of bias. Our reassuring clinical results are all based on a classic technique of fat grafting derived from the Coleman technique. No matched control clinical study has been published regarding enrichment

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techniques. Only one retrospective study, without a control group, with a small number of patients, and with a very short follow-up (1 year), has been published. These techniques produce a concentration of progenitor cells in the specimen that is injected, providing improvement of the healing process as demonstrated by Pérez-Cano et al.[15,16] It would be worthwhile proving that such an increased concentration does not stimulate the remaining cancer cells in the tumor bed. Another technique of stimulation of progenitor cell activity by the use of growing factors has also been proposed to improve the healing process of the fat graft[17] but, again, it would be necessary to perform controlled studies to prove that the growing factors are not stimulating the remaining cancer cells in the tumor bed. Moreover, breast conservative treatment provides a higher risk of cancer cells remaining in the treated breast despite the adjuvant radiotherapy. The fat grafting could stimulate such dormant cancer cells, increasing the risk of subsequent local recurrences.[18] To evaluate such risk, we performed a matched control study on 322 breast conservative treatment patients undergoing subsequent fat grafting compared with 322 breast conservative treatment patients without fat grafting.

PATIENTS AND METHODS

Technique of Fat Grafting

At present, the technique used in our Institute was published in 1995 by Coleman. Aspirated fat tissue is taken, centrifuged, and injected into the area where 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. The purified fat is then reinjected with a 3- or 10-cc syringe and a small amount of fat at each injection. It is important not to inject a large bolus of fat at the same place to avoid necrosis of the specimen. The smaller the "spaghettis" of fat tissue injected, the better the chance of revascularization and the lower the risk of necrosis. Moreover, the degree of reabsorption of the injected adipose tissue is unpredictable.[19] Rigotti et al. demonstrated that fat grafting is more than just a filler: it also enhances skin trophicity, which is interesting after radiotherapy.[20]

In our study, 316 of 322 patients received only one injection of fat grafting, five received two injections, and one received three injections. For most of them, injection was performed at the level of the tumor bed. The amount of fat injected was 20 to 190 cc, with a mean of 90 cc.

Selection of Cases

All patients with previously treated primary invasive breast cancer, who subsequently underwent fat grafting from 2006 to 2013 at the European Institute of Oncology and were free of events at the time of fat grafting, were selected as cases.

Selection of Controls

To account for the delay between breast cancer surgery and fat grafting, cases were individually matched (1:1 ratio) to controls operated on for invasive breast cancer during the same period. The controls did not receive fat grafting, remained free of any event for a period corresponding to the delay between breast cancer surgery and fat grafting of the index case, and had otherwise similar characteristics as the index case (i.e., age, size of the tumor, number of positive lymph nodes, estrogen receptor status, Ki-67 proliferative labeling index, HER-2 overexpression status, use of neoadjuvant chemotherapy, and type of adjuvant radiotherapy).

Statistical Analysis

For all cases, the disease-free interval between breast cancer surgery and fat grafting was calculated. Follow-up was considered from the time of fat grafting for the cases or from its equivalent time for controls (i.e., the time of surgery plus the corresponding disease-free interval of the index case). The yearly incidence of breast-related events (ipsilateral breast cancer recurrence, axillary or regional lymph node metastasis, distant metastasis, contralateral breast cancer, other primary breast cancer, and death as first event) and total deaths was calculated by dividing the number of events in each group by the total number of person-years of observation accumulated until the date of the last visit (for breast-related events) or until the date of last assessment of vital status (for deaths). Disease-free survival and overall survival plots were drawn using the Kaplan-Meier method. The log-rank test was used to assess the survival difference between the two groups. All analyses were performed with SAS Version 9.2 (SAS Institute, Inc., Cary, N.C.). All p values were two-sided.

RESULTS

Patient characteristics are listed in Table 1. Cases and controls exhibit very similar characteristics because of the 1:1 individual matching for most of the variables.

During a mean observation time of 4.8 years (fat grafting group) (range, 0.1 to 9.6 years) and 4.4 years (control group) (range, 0.1 to 10.2 years)

Table 1. Patient Characteristics (Matching Variables)

	Fat Grafting	Control	*p*
No. of patients	322	322	
Age			
<35 yr	32	26	
35–39 yr	57	60	
40–44 yr	70	68	
45–49 yr	72	76	
≥50 yr	91	92	0.93
Year of surgery			
<2000	11	12	
2000–2004	113	115	
2005–2009	167	164	
2010–2012	31	31	0.99
pT			
pT0–1	242	242	
pT2	75	76	
pT3–4	4	2	
pTx	1	2	0.80
Positive nodes			
0	189	190	
1	59	62	
2	24	26	
≥3	49	43	
pNx	1	1	0.97
ER			
Negative	44	44	
Positive	277	277	
n/d	1	1	1.00
Ki-67			
<20	155	155	
≥20	166	164	
n/d	1	3	0.60
HER-2			
0/+/++	267	266	
+++	44	44	
n/d	11	12	0.98
Subtype			
Luminal A	95	86	
Luminal B	184	187	
Her2	11	13	
Triple-negative	27	27	
n/d	5	9	0.78
Neoadjuvant CT			
No	299	299	
Yes	23	23	1.00
RT			
None	6	5	
Eliot	269	271	
External RT	47	46	0.95

pT, size of the tumor; pTx, size unknown; pNx, Unknown status of the axilar nodes; n/d, not determined; CT, computed tomography; RT, radiation therapy; ELIOT, external radiotherapy for early breast cancer.

after the date of fat grafting (or index date), 40 patients in the fat grafting group and 40 patients in the control group developed a first event ($p = 0.59$, log-rank test) (Table 2 and Fig. 1). No difference was observed for the development of ipsilateral breast cancer recurrence (14 cases and 16 controls; $p = 0.49$, log-rank test), axillary or regional lymph node metastasis (three cases and six controls; $p = 0.23$, log-rank test), distant metastasis (14 cases and 15 controls; $p = 0.67$, log-rank test), contralateral breast cancer (four cases and five controls; $p = 0.51$, log-rank test), other primary breast cancer (10 cases and four controls; $p = 0.16$, log-rank test), or death as a first event (zero cases and one control; $p = 0.30$, log-rank test). Three patients in the fat grafting group and six patients in the control group died during follow-up ($p = 0.25$, log-rank test) (Table 2 and Fig. 1).

DISCUSSION

To assess the cancer safety of fat grafting in breast cancer patients, we retrospectively compared 322 patients receiving breast conservative treatment followed by fat grafting and 322 matched patients with similar characteristics who did not undergo fat grafting. Our results confirm the absence of a significant difference between the two groups when comparing the incidence of locoregional events, distant metastases, or death.

In our previous matched case-control study at the European Institute of Oncology, we did not find any statistical differences in the incidence of locoregional event between the two groups.[21] In our second study comparing fat grafting in patients with in situ breast cancer with a control group, a higher statistical difference was observed in the study group. However, recently, an unpublished analysis of the same series of patients did not find a statistical difference after a longer follow-up.[22] In the literature, three matched case-control studies have been published that did not reveal any increasing risk of local recurrences in their fat grafting group. Rigotti et al.[23] reported the results of a series of 137 mastectomies followed by fat grafting. The cancer safety was evaluated by comparing the risk of local recurrence between mastectomy and fat grafting to the risk observed in the period after fat grafting. The rate of recurrence after breast cancer treatment decreases spontaneously with time, reaching a plateau after several years, providing a bias for the comparison of the local recurrence risk in the two periods.[24] Moreover, the study was focused only on mastectomy cases and did not analyze the results of fat grafting in breast conservative treatment patients, where the risk of remaining cancer cells in the breast tissue could be stimulated by the fat tissue stem cells.

The second study was published by Gale et al.[25] They used a protocol similar to ours for comparison with the controls. The study gathered 211 lipofilling cases. Among these cases, 27 were in situ (13 percent) and 184 were invasive (87 percent), and 176 underwent mastectomy (83.4 percent) and 35 underwent breast conservative treatment (16.6 percent). The lipofilling patients were matched (2:1) to the control population.

Table 2. Events Observed during Follow-Up

	Fat Grafting (rate/100 yr)	Control (rate/100 yr)	*p* (log-rank)
No. of patients	322	322	
No. of person-years until last visit	1545	1401	
No. of person -years until last assessment of vital status	1645	1522	
Any first events*	40 (2.59)	40 (2.86)	0.59
Ipsilateral breast tumor recurrence*	14 (0.91)	16 (1.14)	0.49
Axillary/regional lymph node metastasis	3 (0.19)	6 (0.43)	0.23
Distant metastasis*	14 (0.91)	15 (1.07)	0.67
Contralateral breast cancer	4 (0.26)	5 (0.36)	0.51
Other primary cancer†	10 (0.65)	4 (0.29)	0.16
Death as first event	0 (0.00)	1 (0.07)	0.30
Total deaths	3 (0.18)	6 (0.43)	0.25

*Four patients in each group developed ipsilateral breast tumor recurrence and distant metastasis simultaneously; 1 patient in the fat grafting group and 3 in the control group developed ipsilateral breast tumor recurrence and lymph node metastasis simultaneously.
†Includes cancer of the thyroid ($n = 2$), fallopian tube ($n = 1$), ovary ($n = 1$), endometrium ($n = 1$), melanoma ($n = 1$), rectum ($n = 1$), sarcoma ($n = 1$), non-Hodgkin lymphoma ($n = 1$), and occult cancer ($n = 1$) in the lipofilling group; and cancer of the thyroid ($n = 1$), endometrium ($n = 1$), melanoma ($n = 1$), and leukemia ($n = 1$) in the control group.

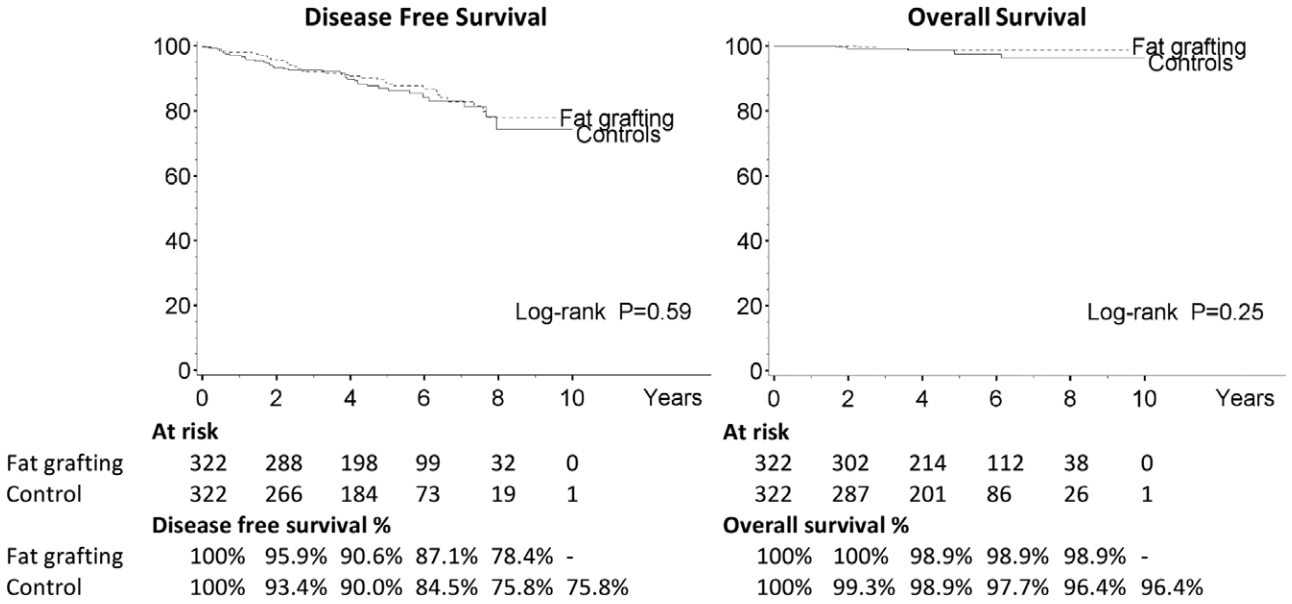

Fig. 1. Disease-free survival (*left*) and overall survival (*right*) after fat grafting (or index date of fat grafting).

Mean follow-up was 88 months from primary cancer surgery and 32 months since fat grafting. The cumulative incidence of a local recurrence (ipsilateral breast or chest wall) in the fat grafting and control groups was 0.95 percent and 1.90 percent, respectively ($p = 0.74$). The locoregional recurrence rate was equal between the fat grafting and control groups [four of 211 (1.9 percent) and eight of 422 (1.9 percent)], 0.7 percent per year.

The third matched case-control study was published by Kronowitz et al.[26] This study gathered 719 breast cancer patients with fat grafting: 9.9 percent underwent breast conservative treatment and 75.3 percent underwent mastectomy, and 67.5 percent were invasive carcinomas and 10.5 percent were in situ cancers. Mean follow-up after mastectomy was 60 months for the fat grafting group and 44 months for controls. The results were nine local recurrences in the fat grafting group and 16 in the controls group (1.3 percent versus 2.4 percent; $p = 0.45$). Although the two groups were not perfectly matched,[27] the large number of patients in the series provides a good argument in favor of the safety of fat grafting.

CONCLUSIONS

Despite animal model evidence suggesting a higher risk of tumor progression with fat grafting, our matched controlled study brings a solid argument in favor of the safety of fat grafting in breast cancer patients. However, additional clinical

studies could be desirable to further confirm the cancer safety of fat grafting.

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