Oncologic Safety of Autologous Fat Grafting after Breast Cancer Surgical Treatment: A Matched Cohort Study

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PATIENT SAFETY

3 THERAPEUTIC

Background: Autologous fat grafting has been an increasingly popular procedure for remodeling the breast of patients undergoing breast cancer surgery. This study's objective was to investigate whether autologous fat grafting is associated with a higher risk of disease recurrence in the context of late breast reconstruction for patients diagnosed with breast cancer who have undergone either breast-conserving surgery or mastectomy.

Methods: A retrospective matched cohort study was performed in a single tertiary health care center. Data were collected from 42 patients formerly treated for breast cancer who underwent the first session of autologous fat grafting between August of 2007 and June of 2016. A total of 126 patients with similar features, who did not undergo autologous fat grafting, were individually matched at a 1:3 ratio with the autologous fat grafting group. The primary endpoint was locoregional recurrence. Secondary outcomes were rates of local and distant recurrences, disease-free survival, and overall survival.

Results: At a mean follow-up of 65 months after fat grafting, no significant differences were found between the lipofilling and control groups for locoregional recurrence (7.1 percent versus 6.3 percent; $p = 0.856$), local recurrence (7.1 percent versus 5.6 percent; $p = 0.705$), distant recurrence (14.3 percent versus 7.9 percent; $p = 0.238$), disease-free survival (21.4 percent versus 19.0 percent; $p = 0.837$), and overall survival (14.3 percent versus 7.1 percent; $p = 0.181$).

Conclusions: No evidence of increased risk in any of the survival outcomes was identified. Lipofilling seems to be a safe procedure for breast reconstruction after surgical treatment of breast cancer. (*Plast. Reconstr. Surg.* 148: 11, 2021.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Autologous fat grafting has been an increasingly popular procedure for remodeling the breast of patients undergoing breast cancer surgery,[1] either in a delayed or immediate fashion, and for both mastectomy and conservative operations.[2–6] It allows correction of subtle breast defects that could not be achieved with the use of implants alone or other reconstructive procedures,[7] leading to a significant aesthetic improvement in symmetry, contour, volume, and decreased stiffness of the scar,[8] with a high grade of both patient and surgeon satisfaction.[2,8–10] Apart from enhancing aesthetic outcomes, autologous fat grafting also impacts the quality of life of these survivor patients by improving psychological and sexual well-being and alleviating chronic pain around the surgical site where it is applied.[11]

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Several techniques were designed to collect and process the adipose tissue to be used for grafting, and the most applied is the one described by Coleman.[7,12] There is a variety of cell types obtained from the adipose tissue collected by liposuction: adipocytes, adipose stem cells, preadipocytes, fibroblasts, vascular endothelial cells, and a diversity of immune system cells. Among them, the adipose stem cells represent approximately 1 to 2 percent of the cell population.[13] They stimulate the regeneration of injured tissues by developing a new microenvironment by releasing cytokines ("adipokines"), chemokines, hormones, and growth factors. Preclinical data suggest that transferring these cells to a previous cancer site could stimulate the activation of adjacent latent cancer cells.[14,15] Experimental studies—in vivo and in vitro—show that certain cancer cell lines, combined with human donor adipose-derived stem cells, can integrate with tumor stroma, exacerbating cancer cell carcinogenesis and progression, leading to the development of larger and more vascularized tumors.[14]

Even though some experimental studies have shown unfavorable results to that issue, clinical studies have demonstrated favorable results for its safety after breast cancer surgical treatment.[16–24] Since the American Society of Plastic Surgeons Fat Graft Task Force's statement about the safety and efficacy of autologous fat grafting published in 2009,[25] acknowledging the lack of information to guide proper patient selection and recommendation on potential complications and outcomes, numerous studies concerning its oncologic safety have been reported.[15,26–29] Nonetheless, no clinical trials have been outlined to answer this issue, as it is a great challenge to settle on an appropriate study design because there is still no other comparable reconstructive option with similar applicability. Therefore, setting a control group without an alternative would be somewhat unethical.[28,30] The more reliable studies so far are matched cohorts.[15,26–29,31–33] The first one was published in 2012,[27] setting up a control group with matched baseline characteristics to ensure homogeneity of risk factors between groups, decreasing the potential impact of underlying confounding variables, which could have led to a biased risk assessment. Other cohorts with similar study designs were reported afterward,[15,28,29,31–33] and a meta-analysis published in 2018,[34] including them, showed favorable outcomes concerning its safety. However, most of them had a somewhat short median follow-up time of approximately 2 to 3 years after fat grafting[15,27,29,31,33]—a unique matched cohort included had a median follow-up of at least 5 years.[28] This study aims to assess the oncologic safety of autologous fat grafting as a late reconstruction procedure in breast cancer patients, after either breast-conserving surgery or mastectomy, with at least 5 years of follow-up.

MATERIALS AND METHODS

Based on the results from Krastev et al. in 2019,[28] we performed a sample size estimate for an adequate power to detect a difference in locoregional recurrence rates between fat grafting exposed and nonexposed patient groups, setting up a significance level of 5 percent and a statistical power of 80 percent, resulting in an estimate of a minimum of 4813 patients for each group. After the Institutional Ethics Committee approved the study under the number 1606/2018, we retrospectively identified through a prospectively maintained database of Barretos Cancer Hospital, a tertiary health care center, all consecutive patients that underwent autologous fat grafting after breast cancer surgical treatment, clinical stages 0, I, II, and III—either conservative surgery or mastectomy—associated or not with other methods of breast reconstruction, from the first procedure performed at the institution on August of 2007, until June of 2016. (No informed consent was applied because of the retrospective nature of the study. This study's researchers are committed to preserving the privacy of participants, ensuring that the data collected will be used solely and exclusively for this work and that the information disclosed will in no way identify the research participant.) The lipofilling procedure was performed according to Coleman's technique[7] with minor differences, without graft enrichment with regenerative cells derived from adipose tissue.[35] Exclusion criteria were as follows: benign conditions; bilateral carcinoma; absence of free margins on tumor resection; risk-reducing prophylactic surgery; oncologic surgery performed in another institution with insufficient clinical, pathologic, and treatment data; unfeasibility of locoregional treatment with radiotherapy when indicated; and development of locoregional recurrence, distant recurrence, or both between primary surgical treatment and fat grafting.

After that, through the Barretos Cancer Hospital database, patients were selected for the control group, defined as patients with breast cancer surgical treatment, and who subsequently did not undergo fat grafting, among available breast reconstructive procedures. Controls were individually matched for features similar to their

respective cases, as performed by Petit et al.[27] All of the following characteristics were necessarily matched (Table 1): age (within 5 years), date of oncologic surgery (within 2 years), surgery type (breast-conserving surgery or mastectomy), histologic type (invasive ductal carcinoma, invasive lobular carcinoma, or ductal carcinoma in situ), and hormone receptor status (estrogen or progesterone receptor expression positivity or negativity). A list of all possible controls was established for each respective case, and subsequently controls were selected by lot at a 3:1 ratio.

The deadline for the inclusion of follow-up data was August 31, 2018. As the study intervention was fat grafting, the baseline date considered for patient follow-up analysis and comparison of survival and relapse outcomes was established as the date of the first grafting session for the fat grafting group. For proper comparison, the control group patients' baseline date commenced at the same interval between oncologic surgery and the first lipofilling session of their respective case. Control group patients had a follow-up of at least the same range from oncologic surgery to the first grafting session of their respective cases (Fig. 1). Neither group could develop any event during this period. If they did, that patient was excluded from the study.

Table 1. Baseline Characteristics, Including Matched Variables

	Fat Grafting (%)	Control (%)	*p*
No. of patients	42	126	
Mean age at cancer surgery ± SD, yr	45 ± 9	46 ± 8	0.383
Mean age at baseline ± SD, yr	50 ± 9	52 ± 9	0.203
Time A–B, mo			1.000
Median	51	51	
IQR	32–74	32–74	
Year of oncologic surgery			0.811
2000–2004	12 (28.6)	31 (24.6)	
2005–2009	22 (52.4)	66 (52.4)	
2010–2014	8 (19.0)	29 (23.0)	
Type of surgery			1.000
BCS	22 (52.4)	66 (52.4)	
Mastectomy	20 (47.6)	60 (47.6)	
Histology			1.000*
DCIS	1 (2.4)	3 (2.4)	
IDC	39 (92.9)	117 (92.9)	
ILC	2 (4.8)	6 (4.8)	
Hormone receptor status			1.000
Negative	14 (32.3)	42 (32.3)	
Positive†	28 (66.7)	84 (66.7)	

IQR, interquartile range; BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.
*Calculated by Fisher's exact test.
†Positivity for estrogen and/or progesterone receptor expression.

The primary outcome was to evaluate its safety by comparing locoregional recurrence rates between patients exposed and not exposed to fat grafting. The secondary outcomes were local recurrence, distant recurrence, disease-free survival, and overall survival. Local recurrence was defined as the interval from baseline to the first recurrence of ipsilateral breast or chest wall tumors. Regarding secondary outcomes, locoregional recurrence was defined as the interval between baseline and first ipsilateral tumor recurrence in the breast or chest wall, or supraclavicular, infraclavicular, axillary or internal mammary lymph node involvement. Disease-free survival was defined as the interval from baseline to the occurrence of any first event—local, regional, or distant relapses; development of a second noninvasive primary breast cancer; contralateral breast cancer; or death from any cause. Overall survival was defined as the interval from baseline to death from any cause. If none of the above events occurred, data collection was censored at the last follow-up. In cases of patients undergoing more than one grafting procedure and developing any of the above events, the time interval from baseline up to the first event was established from the first session performed. Moreover, we conducted some additional analyses assessing whether the number of autologous fat grafting sessions performed and the type of surgery impact the risk of locoregional recurrence.

All patients had outpatient consultations at the usual follow-up of breast cancer after definitive oncologic surgery and after autologous fat grafting. In patients free of any first event, follow-up was performed every 6 months for the first 5 years and annually thereafter. Control mammograms were obtained annually, on only the remaining breast if the patient underwent mastectomy, commencing a minimum of 6 months after cancer surgery or radiotherapy. If there was clinical suspicion of relapse, abnormal physical examination, or abnormal mammography, an investigation was continued as appropriate. To ensure an adequate design of observational research and also an appropriate report of results obtained, the recommendations described by the Strengthening the Reporting of Observational Studies in Epidemiology statement were followed.[36]

Statistical Analysis

For the descriptive analysis of categorical variables, frequency and percentage were calculated. To compare categorical variables by groups, the chi-square test was used. If necessary, Fisher's

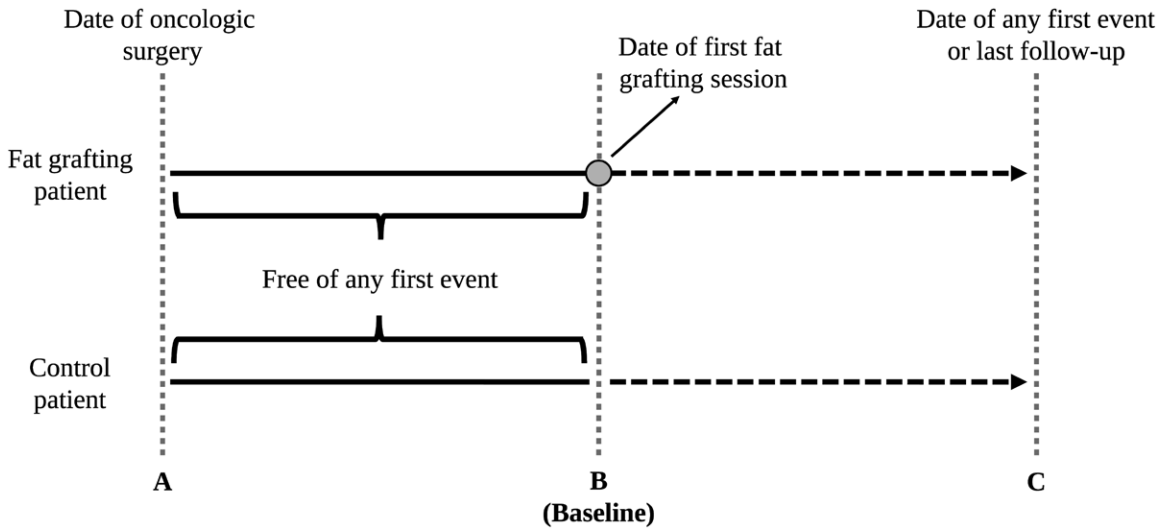

Fig. 1. Matched cohort study design. (Adapted from Petit JY, Botteri E, Lohsiriwat V, et al. Locoregional recurrence risk after lipofilling in breast cancer patients. *Ann Oncol*. 2012;23:582–588, with permission from Elsevier.)

exact test was used. The normal distribution of continuous variables was assessed initially using the Shapiro-Wilk test for the lipofilling group and the Kolmogorov-Smirnov test for the control group. If a nonnormal distribution of variables was observed, for the descriptive analysis, medians and interquartile ranges were calculated, and to compare variables by groups, the Mann-Whitney nonparametric test was applied. If there was a normal distribution, for the descriptive analysis, mean and standard deviation were calculated, and to compare variables by groups, the *t* test was performed. Survival curves were estimated by the Kaplan-Meier method and comparison between groups by log-rank test. For the analysis of the interaction between type of surgery and autologous fat grafting in locoregional recurrence, the generalized linear model was used. A significance level of 5 percent ($p < 0.05$) was established. Analyses were performed using IBM SPSS Version 20.0 (IBM Corp., Armonk, N.Y.).

RESULTS

In the first step, all patients undergoing lipofilling at Barretos Cancer Hospital were identified. Between August of 2007 and June of 2016, we identified 54 patients, and 10 of them were excluded: three without a breast cancer diagnosis, two with local recurrence before lipofilling, and five with distant metastases before lipofilling. Subsequently, a proportion of three controls were obtained for each fat grafting patient. For two patients that underwent lipofilling, no adequate controls were obtained. Thus, for statistical analysis and presentation of results, data from 168 patients were used: 42 fat grating patients and 126 control patients (Fig. 2).

The matched variables are presented in Table 1. Other observed and unmatched variables are presented in Tables 2 through 4, assessing anatomopathologic characteristics, complementary treatments, and follow-up periods, respectively. Homogeneity of features was identified among them, with no significant differences in the distribution of variables. Most patients were diagnosed with early breast cancer, with clinical stages I and II representing 32 of 42 (76.2 percent) in the fat grafting group and 101 of 126 (80.1 percent) in the control group. T2 - T4

The Her-2 status assessment by immunohistochemical test commenced before the introduction of Her-2 targeted therapy at the institution in 2010. Her-2–positive breast cancers were identified by immunohistochemical staining in nine patients in the autologous fat grafting group (21.4 percent) and in 23 controls (18.4 percent). However, only two patients in the autologous fat grafting group (4.8 percent) and two controls (1.6 percent) were treated with trastuzumab, because most of them were diagnosed with breast cancer before 2010.

In our study, patients who underwent neoadjuvant chemotherapy had locally advanced breast cancer (clinical stage IIIA to IIIC), except two patients in the control group, who had clinical stage IIA (cT2m cN0) and IIB (cT2 cN1) breast cancer. Both underwent mastectomy after neoadjuvant systemic treatment. Only

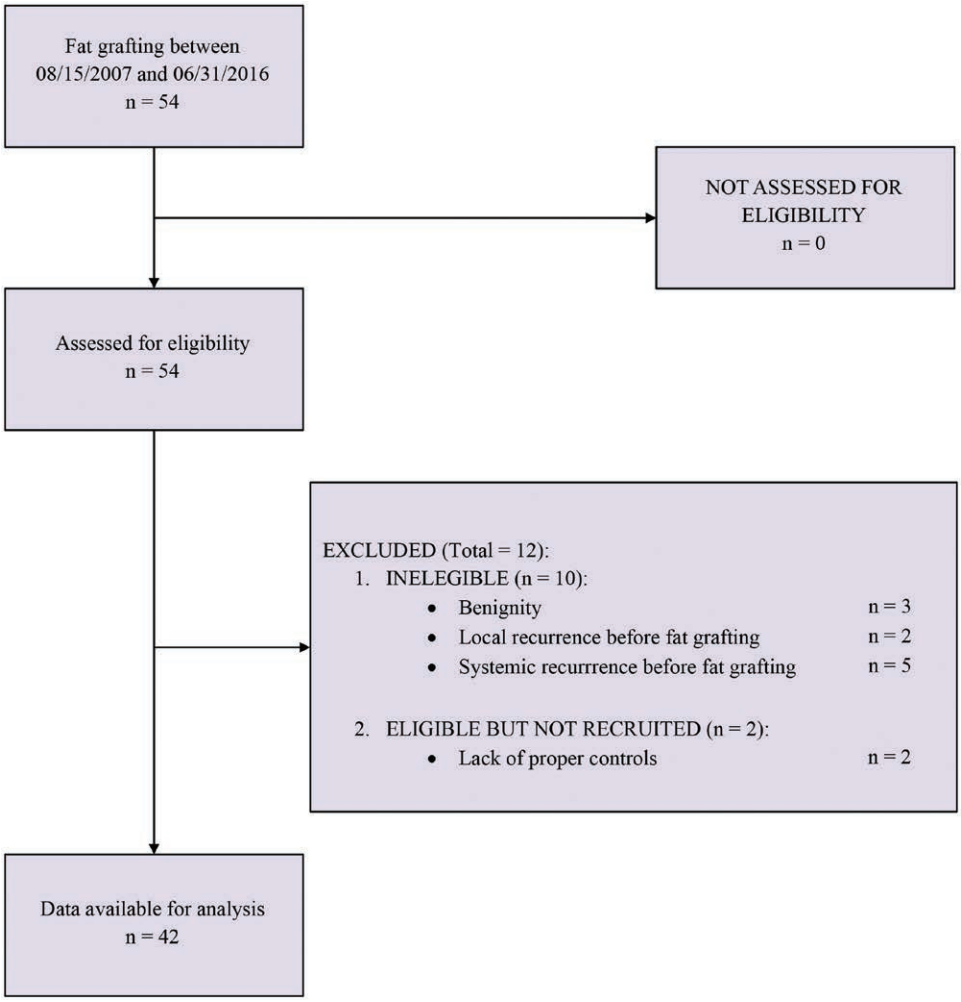

Fig. 2. Flow diagram for fat grafting patients' selection.

one patient in each group underwent breast-conserving surgery after neoadjuvant chemotherapy. The patient in the control group was a matched control for the one who underwent breast-conserving surgery in the autologous fat grafting group.

F3, F4 Data from survival outcomes are shown in Table 5 and Figures 3 and 4. (**See Figure, Supplemental Digital Content 1**, which shows local recurrence from baseline, ***http://links.lww.com/PRS/E469***. **See Figure, Supplemental Digital Content 2**, which shows distant recurrence from baseline, ***http://links.lww.com/PRS/E470***. **See Figure, Supplemental Digital Content 3**, which shows overall survival from baseline, ***http://links.lww.com/PRS/E471***.) There were no significant differences for any of the analyzed outcomes over an average follow-up period of 5.4 years. Cumulative local recurrence incidences were 7.1 percent for the fat grafting group and 5.6 percent for the control group (p = 0.705), locoregional recurrence rates were 7.1 percent for the fat grafting group and 6.3 percent for the control group (p = 0.856), and distant recurrence rates were 14.3 percent and 7.9 percent, respectively (p = 0.238). There was only one patient among controls who had a regional recurrence, and none among the fat grafting group; there was no significant difference between groups. Disease-free survival rates were 78.6 percent in the fat grafting group and 81.0 percent in the control group (p = 0.837), and overall survival rates were 85.7 percent and 82.9 percent, respectively (p = 0.181). Other observed events are presented in Table 5. Except for one control group patient who evolved to death associated with the evolution of colon adenocarcinoma disease, all other causes of mortality were associated with breast cancer in both fat grafting and control groups.

The comparison of locoregional recurrence by the number of autologous fat grafting sessions performed is presented in Table 6. For this

Table 2. Nonmatched Baseline Variables

	Fat Grafting (%)	Control (%)	*p*
No. of patients	42	126	
Nuclear grade†			0.779*
1	2 (4.8)	5 (4.0)	
2	14 (33.3)	33 (26.2)	
3	8 (19.0)	30 (23.8)	
Unknown	18 (42.9)	58 (46.0)	
Histologic grade†			0.377*
1	5 (11.9)	12 (9.5)	
2	21 (50.0)	70 (55.6)	
3	11 (26.2)	38 (30.2)	
Unknown	5 (11.9)	6 (4.8)	
Estrogen receptor status			0.524
Negative	15 (35.7)	52 (41.3)	
Positive	27 (64.3)	74 (58.7)	
Progesterone receptor status†			0.826
Negative	18 (42.9)	56 (44.8)	
Positive	24 (57.1)	69 (55.2)	
Her-2 status†			0.548
Negative (0/1+)	28 (66.7)	78 (62.4)	
Equivocal (2+/3+)	5 (11.9)	24 (19.2)	
Positive (3+/3+)	9 (21.4)	23 (18.4)	
Ki-67†			1.000*
<14%	2 (4.8)	6 (4.8)	
≥14%	6 (14.3)	17 (13.5)	
Unknown	34 (81.0)	103 (81.7)	
Clinical stage			0.818*
0	1 (2.4)	3 (2.4)	
I	11 (26.2)	42 (33.3)	
II	21 (50.0)	61 (48.4)	
III	9 (21.4)	20 (15.9)	
Tumor size			0.974*
Tis	1 (2.4)	3 (2.4)	
T1	12 (28.6)	39 (31.0)	
T2	20 (47.6)	56 (44.4)	
T3	5 (11.9)	18 (14.3)	
T4	4 (9.5)	10 (7.9)	
Pathologic lymph node involvement‡			0.851*
pN0	27 (65.9)	86 (68.3)	
pN1	12 (29.3)	35 (27.8)	
pN2–pN3	2 (4.9)	5 (4.0)	

*Calculated by Fisher's exact test.
†Missing information on some patients: nuclear grade [fat grafting, 18 (42.9%); control, 58 (46.0%)], histologic grade [fat grafting, five (11.6%); control, six (4.7%)], progesterone receptor [control, one (0.8%)], Her-2 status [control, one (0.8%)], and Ki-67 [fat grafting, 35 (81.4%); control, 106 (82.2%)].
‡One patient with ductal carcinoma in situ diagnosis did not undergo the axillary approach.

analysis, two categories were used: one autologous fat grafting session (n = 30) or greater than or equal to two sessions (n = 12). There was no significant difference in locoregional recurrence risk by the number of autologous fat grafting sessions performed (p = 1.00). Data for the analysis of the interaction between type of surgery and group (i.e., undergoing or not an autologous fat grafting procedure) are listed in Table 7. There was no significant interaction between type of surgery and group in the risk of locoregional recurrence (p = 0.781).

Table 3. Complementary Treatments: Nonmatched Variables

	Fat Grafting (%)	Control (%)	*p*
No. of patients	42	126	
Chemotherapy			0.768*
No	5 (11.9)	12 (9.5)	
Yes	37 (88.1)	114 (90.5)	
Neoadjuvant chemotherapy			0.805
No	35 (83.3)	107 (84.9)	
Yes	7 (16.7)	19 (15.1)	
Adjuvant chemotherapy			0.831
No	10 (23.8)	28 (22.2)	
Yes	32 (76.2)	98 (77.8)	
Radiotherapy			0.230*
No	4 (9.5)	5 (4.0)	
Yes	38 (90.5)	121 (96.0)	
Trastuzumab			0.260*
No	40 (95.2)	124 (98.4)	
Yes	2 (4.8)	2 (1.6)	
Endocrine therapy			0.851
No	15 (35.7)	43 (34.1)	
Yes	27 (64.3)	83 (65.9)	
Tamoxifen			0.785
No	16 (38.1)	51 (40.5)	
Yes	26 (61.9)	75 (59.5)	
Anastrozole			0.566*
No	39 (92.9)	111 (88.1)	
Yes	3 (7.1)	15 (11.9)	

*Calculated by the Fisher's exact test.

Table 4. Follow-Up

	Fat Grafting	Control	*p*
No. of patients	42	126	
Follow-up			
Mean time since cancer surgery ± SD, mo	122 ± 43	121 ± 38	0.880
Time to baseline, mo			1.000
Median	51	51	
IQR	32–74	32–74	
Mean time since baseline ± SD, mo	65 ± 35	65 ± 35	0.930

IQR, interquartile range.

Table 5. Events Observed during Follow-Up

	Fat Grafting (%)	Control (%)	*p* (log-rank)
No. of patients	42	126	
Local recurrence*	3 (7.1)	7 (5.6)	0.705
Locoregional recurrence*	3 (7.1)	8 (6.3)	0.856
Systemic recurrence*	6 (14.3)	10 (7.9)	0.238
Contralateral breast cancer*	3 (7.1)	7 (5.6)	0.738
Other primary cancer *†	0 (0)	4 (3.2)	0.243
Death as first event	0 (0)	0 (0)	1
Any first event	9 (21.4)	24 (19.0)	0.837
Total deaths	6 (14.3)	9 (7.1)	0.181

*Two patients in the fat grafting group developed local and contralateral breast recurrence simultaneously, and one of them had distant metastasis (bone) later; one control patient developed local recurrence and contralateral breast cancer later; one control patient developed regional and distant recurrence (pulmonary) simultaneously; one control patient developed contralateral and distant metastasis (bone) simultaneously; and one control patient developed other primary cancer (endometrium) and local recurrence later.
†Includes cancer of the endometrium (n = 1), parotid (n = 1), and colon (n = 2).

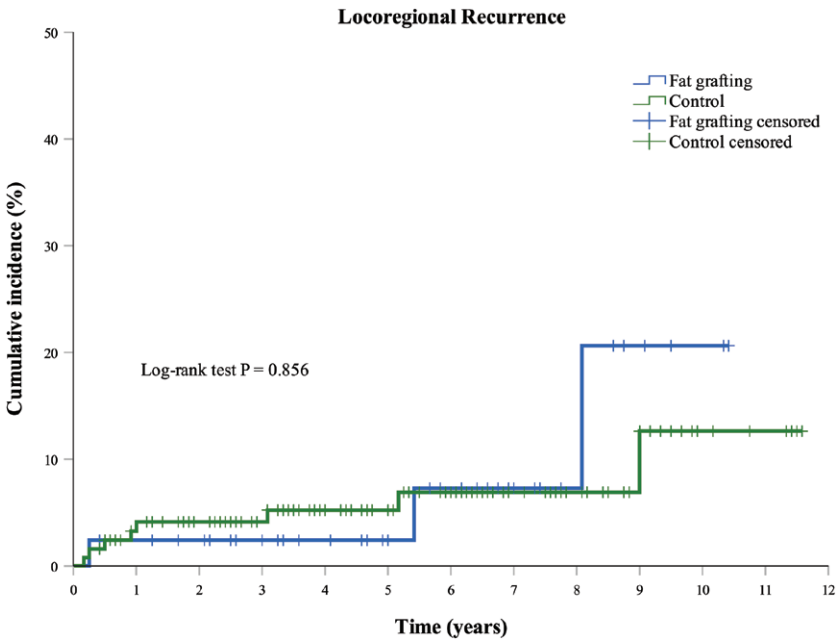

Fig. 3. Locoregional recurrence from baseline.

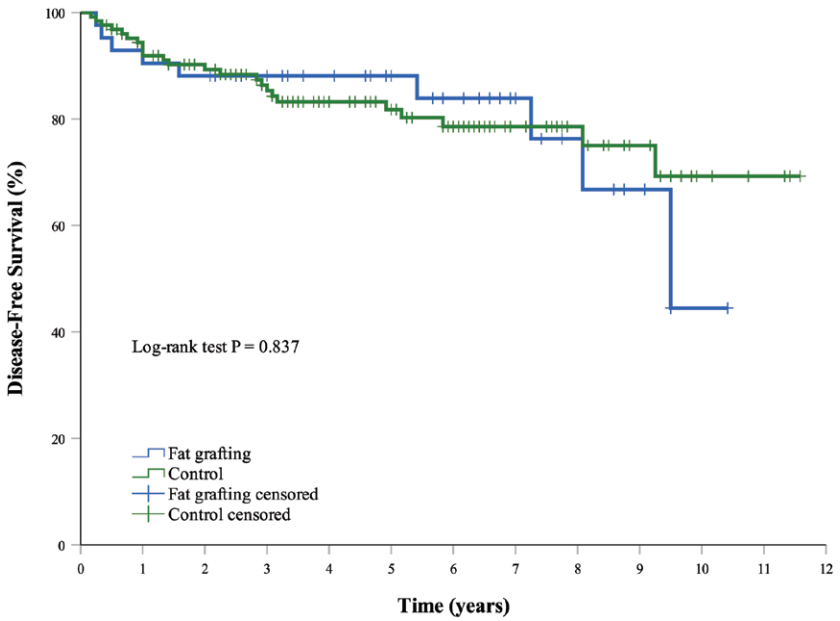

Fig. 4. Disease-free survival from baseline.

DISCUSSION

In agreement with prior clinical studies, there were no significant differences in rates of local, locoregional, and distant recurrence. In both groups, most patients had estrogen receptor–positive tumors, which was also observed in most previous cohorts, a profile that may recur later in the disease course, either locoregional or distant recurrence.[37,38] For more reliable evidence about oncologic safety, a longer follow-up period is expected after lipofilling to assess whether recurrence is associated with this feature. Conversely, most matched cohorts had a somewhat short mean follow-up time—around 2 to 3 years.[15,27,29,31,33] This study has one of the longest mean follow-up times after fat grafting (65 months for both groups) (Table 8), and to our knowledge, only two others reached at least a mean 5-year period.[26,28]

A unique matched cohort—including only patients diagnosed with carcinoma in situ

Table 6. Locoregional Recurrence by Number of Autologous Fat Grafting Sessions Performed

	LRR		
	No (%)	Yes (%)	*p**
No. of patients	39	3	
No. of AFG sessions			1.000
1	28 (93.3)	2 (6.7)	
≥2	11 (91.7)	1 (8.3)	

LRR, locoregional recurrence; AFG, autologous fat grafting.
*Calculated by Fisher's exact test.

disease—noted unfavorable outcome concerning oncologic safety.[31] A higher risk of local recurrence was observed after a median follow-up of 38 and 42 months from baseline, respectively, for the lipofilling and control groups (5-year cumulative incidence of local recurrence of 18 percent and 3 percent, respectively; $p = 0.02$). In a subgroup analysis, autologous fat grafting increased the risk of local recurrence in high-grade tumors, in women younger than 50 years, in those undergoing quadrantectomy, and in those with a Ki-67 value greater than or equal to 14 percent. In a later study—assessing another series of patients—Petit et al.[32] highlight that the former series did not show a statistical difference after a longer follow-up. Therefore, there are no more matched cohorts reporting unfavorable oncologic outcomes. Although current data have not yet been published, this fortifies the premise that a follow-up of approximately 3 years after exposure to autologous fat grafting may still be too short to reliably assess the oncologic safeness, which includes most of the published reports. In our study, there was only one case and three respective matched controls diagnosed with ductal carcinoma in situ.

Table 7. Locoregional Recurrence by Group versus Type of Surgery

	LRR				*p*		
	Fat Grafting		Control				
	No (%)	Yes (%)	No (%)	Yes (%)	Type of Surgery	AFG	Interaction
Type of surgery							
BCS	20 (90.9)	2 (9.1)	60 (90.9)	6 (9.1)	0.261	0.781	0.781
Mastectomy	19 (95)	1 (5)	58 (96.7)	2 (3.3)			
No. of patients	39 (92.9)	3 (7.1)	118 (93.7)	8 (6.3)			

LRR, locoregional recurrence; AFG, autologous fat grafting; BCS, breast-conserving surgery.

Table 8. Comparison between Matched Cohort Studies

	No. of Patients		Mean Follow-Up Time A–B (mo)	Mean Follow-Up Time B–C (mo)		LRR		DR	
Reference	L	C		L	C	L	C	L	C
This study	42	126	56	65	65	3 7.1%* 1.31%†	8 6.3%* 1.17%†	6 14.3%* 2.63%†	10 7.9%* 1.46%†
Krastev et al., 2019[28]	287	300	51.6	60	52.8	8 2.8%* 0.53%†	11 3.7%* 0.83%†	22 7.7%* 1.46%†	21 7.0%* 1.58%†
Petit et al., 2017[32]	322	322	—	58	53	17 5.3%* 1.09%†	22 6.8%* 1.54%†	14 4.3%* 0.89%†	15 4.7%* 1.05%†
Silva-Vergara et al., 2017[33]	205	410	48.3	40.4	38.5	7 3.4%* 1.01%†	16 3.9%* 1.21%†	7 4.3%* 1.01%†	15 4.5%* 1.14%†
Fertsch et al., 2017[29]	100	100	40.5	32	31	5 5.0%* 1.87%†	2 2.0%* 0.77%†	2 2.0%* 0.75%†	9 9.0%* 3.48%†
Gale et al., 2015[15]	211	422	54	32	34	4 1.9%* 0.71%†	8 1.9%* 0.66%†	7 3.32%* 1.24%†	11 2.6%* 0.91%†
Petit et al., 2013[31]	59	118	25	38	42	6 10.2%* 3.21%†	3 2.5%* 0.72%†	— — —	— — —
Petit et al., 2012[27]	321	642	31	25	26	13 4.05%* 1.94%†	28 3.73%* 2.01%†	13 4.05%* 1.49%†	27 4.21%* 1.94%†

L, lipofilling group; C, control group; LRR, locoregional recurrence; DR, distant recurrence.
*During follow-up time B–C.
†Incidence per year of follow-up.

Thus, a more comprehensive assessment of that histologic subgroup was not feasible.

Our study had the highest relative proportion of recurrence rates, which is expected, because of a longer follow-up. However, if the incidence rate is analyzed by percentage per year, similar recurrence rates are noticed in comparison to prior cohorts with a similar study design of late breast reconstruction, including autologous fat grafting (Table 8).

The retrospective nature is one of the drawbacks of this study. In contrast, it facilitates case matching. A prospective study design matched by five variables would be difficult to perform. For instance, if one control had any event before baseline, it would have to be excluded, and as a consequence, the respective case and the other controls would have to be excluded too, unless a greater number of potential controls were accrued for each case. Another limitation was the small sample size. We did not reach the prespecified size of the population. Even though no significant differences in recurrence rates between groups were observed, our study was underpowered for assessing an association between autologous fat grafting and disease relapse. Still, we made an effort to collect data from all of the patients who underwent fat grafting at our institution from the first procedure performed (August of 2007) until June of 2016, which was determined to be the cutoff date for the first grafting session, thus allowing a minimum follow-up time of at least approximately 2 years after autologous fat grafting (deadline for follow-up, August of 2018). Over that span, all patients from the autologous fat grafting group were assessed consecutively, reducing the risk of selection bias. Furthermore, to decrease the risk of potential random error over the small sample size, we decided on selecting controls at a 1:3 ratio.

The two major limitations from these matched cohorts—including our study—are relatively short follow-up time after exposure to fat graft and small sample size. Moreover, most of them included mainly patients with early breast cancer and estrogen receptor–positive tumors, features that are known to be associated with a substantial risk of later disease recurrence.[38] As most of them are retrospective in nature, an alternative to enhance the reliability of their outcomes would be to resume the analysis of their oncologic outcomes with a longer follow-up time. Several cohort studies with rigorous and similar methodologies from single institutions with a median follow-up of approximately 5 years from baseline have been published in recent years.[26,28] Nonetheless, if analyzed individually, they have limited sample sizes with insufficient statistical power to safely draw a conclusion on the subject. Although there is a previous systematic review and meta-analysis that included all of the matched cohort studies published until that date,[34] most of them had a somewhat short median follow-up time after fat grafting,[3,15,27,29,31,33] and as new reliable matched cohorts with longer follow-up time were developed afterward,[26] an adequate selection of studies by a new systematic review—which could identify more reliable evidence—and pooled analysis of their data could increase the reliability on this issue, limit some sort of bias and random error from small sample sizes, provide a single estimate with a greater statistical power to generalize conclusions, and even generate new hypotheses from subgroup analyses.

CONCLUSIONS

Despite differences in design, no clinical study showed significant differences in survival outcomes. Through a rigorously matched controlled study and a median follow-up of 65 months after fat grafting, our findings strengthen the data on oncologic safety of using autologous fat grafting as an alternative for breast reconstruction in patients undergoing breast cancer surgical treatment, both after conservative surgery and after mastectomy.

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