Determining the Oncologic Safety of Autologous Fat Grafting as a Reconstructive Modality: An Institutional Review of Breast Cancer Recurrence Rates and Surgical Outcomes

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Background: The increasing use of autologous fat grafting in breast cancer patients has raised concerns regarding its oncologic safety. This study evaluated patient outcomes and tumor recurrence following mastectomy reconstruction and autologous fat grafting.
Methods: Retrospective chart review identified patients who underwent mastectomy followed by breast reconstruction from 2010 to 2015. Eight hundred twenty-nine breasts met inclusion criteria: 248 (30.0 percent) underwent autologous fat grafting, whereas 581 (70.0 percent) breasts did not. Patient demographics, cancer characteristics, oncologic treatment, surgical treatment, surgical complications, local recurrence, and distant metastases were analyzed.
Results: Autologous fat grafting patients and control patients were of similar body mass index, smoking status, and *BRCA* status. Patients who underwent fat grafting were significantly younger than control patients and were less likely to have diabetes, hypertension, or hyperlipidemia. The two groups represented similar distributions of *BRCA* status, Oncotype scores, and hormone receptor status. Patients underwent one to four grafting procedures: one procedure in 83.1 percent, two procedures in 13.7 percent, three in 2.8 percent, and four in 0.4 percent. Mean follow-up time from initial surgery was 45.6 months in the fat grafting group and 38.8 months in controls. The overall complication rate following fat grafting was 9.4 percent. Among breasts undergoing surgery for therapeutic indications, there were similar rates of local recurrence (fat grafting group, 2.5 percent; controls, 1.9 percent; $p = 0.747$). Interestingly, mean time to recurrence was significantly longer in the fat grafting group (52.3 months versus 22.8 months from initial surgery; $p = 0.016$).
Conclusions: Autologous fat grafting is a powerful tool in breast reconstruction. This large, single-institution study provides valuable evidence-based support for its oncologic safety. (*Plast. Reconstr. Surg.* 140: 382e, 2017.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Autologous fat grafting has become an increasingly common technique for breast reconstruction following oncologic resection. Benefits of autologous fat grafting include low complication rates, readily available donor sites with low donor-site morbidity, and the fact that it can be performed in an ambulatory setting. In addition, fat grafting has been shown to improve skin quality, particularly in irradiated fields.[1,2]

Although autologous fat grafting has proven effective for both total and adjunctive breast reconstruction, safety concerns have been raised regarding its use in patients with a history of breast cancer. Transferred fat has the potential to interfere with mammographic surveillance and

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Received for publication November 29, 2016; accepted March 6, 2017.
The first two authors contributed equally to the preparation of this article.

DOI: 10.1097/PRS.0000000000003576

Disclosure: *The authors have no associations or financial disclosures to report that create a conflict of interest with information presented in this article.*

promote cancer recurrence by fostering a cellular microenvironment favorable to proliferation of any residual malignant cells following resection in murine models.[3,4] Although the theoretical risks associated with autologous fat grafting for breast cancer reconstruction are significant, these have not been borne out in clinical studies to date.

Previous studies evaluating the relationship of local tumor recurrence following autologous fat grafting are few, have limited patient follow-up time, and have shown equivocal results. In fact, in 2009, the American Society of Plastic Surgeons set up a task force to assess indications, safety, and efficacy of autologous fat grafting and were unable to provide definitive recommendations concerning cancer risk because of the limited number of available studies.[5] Only one study to date has demonstrated an increased risk of tumor recurrence following oncologic resection for in situ carcinoma of the breast.[6] Conversely, a number of systematic reviews and a recent meta-analysis have failed to demonstrate any association with increased tumor recurrence following autologous fat grafting compared to controls.[7–13] More recently, a study of 719 breasts with 60-month follow-up found no significant increase in locoregional recurrence, distant metastases, or new cancers in patients undergoing autologous fat grafting.[14]

Except for the study by Kronowitz et al. as mentioned above, there is a paucity of other corroborating studies evaluating the relationship between autologous fat grafting and tumor recurrence. Our study aims to evaluate patients at our institution who have undergone autologous fat grafting following mastectomy reconstruction for both surgical outcomes and locoregional and distant breast cancer recurrence.

PATIENTS AND METHODS

After obtaining approval from the New York University Institutional Review Board, retrospective chart review identified patients who underwent oncologic resection for breast cancer or carcinoma in situ, followed by breast reconstruction (tissue expander placement followed by implant or autologous reconstruction, immediate implant reconstruction, and immediate autologous reconstruction), from 2010 to 2015 with and without autologous fat grafting. A total of 524 patients met inclusion criteria, comprising 829 breasts. Of these, 248 breasts (30.0 percent) underwent autologous fat grafting (test group), and 581 breasts (70.0 percent) did not undergo autologous fat grafting (control group). The breasts were further subdivided into therapeutic and prophylactic subgroups depending on whether the mastectomy and subsequent reconstruction were performed for therapeutic indications (cancer) versus prophylactic indications (contralateral cancer with prophylactic mastectomy in nondiseased breast). Within the autologous fat grafting group, 162 breasts were operated on for therapeutic indications versus 86 breasts that were operated on prophylactically. Within the control group, there were 414 breasts operated on for therapeutic indications versus 167 breasts that underwent prophylactic intervention.

The two therapeutic groups and the two prophylactic groups were compared and analyzed for differences in demographics, cancer characteristics, oncologic treatment, surgical treatment, surgical complications, local recurrence, and distant metastases to determine whether autologous fat grafting increases breast cancer recurrence. Patients were then divided into two strata: patients who developed locoregional or distant metastasis versus those who did not, and subsequently analyzed for any factors predisposing to development of recurrence including demographic factors, tumor characteristics, and surgical/medical treatment.

All patients included in the study were evaluated by a general surgeon, medical oncologist, and plastic reconstructive surgeon perioperatively. Patients were excluded from this study if they underwent lumpectomy, and only patients who underwent total mastectomy followed by reconstruction were included.

Medical Therapy

Chemotherapy was administered for histologically proven breast cancer by one of several oncologists at the New York University Cancer Center, according to current practice and ongoing treatment protocols. Treatment most commonly involved the following agents: Adriamycin, cyclophosphamide, paclitaxel, docetaxel, methotrexate, fluorouracil, and doxorubicin. Patients were also evaluated for immunotherapy treatment, hormone therapy, and radiation therapy as indicated by current treatment protocols.

Surgical Technique

Patients were evaluated for their surgical management. Those included in the study underwent mastectomy with or without axillary dissection followed by breast reconstruction. The breast reconstruction techniques used included tissue expander placement followed by implant or autologous reconstruction, direct implant reconstruction, and immediate autologous reconstruction.

The indication for and choice of reconstructive procedure were based on patient and surgeon preference. Patients who underwent fat grafting were analyzed for time between surgery and fat grafting, total volume, fat donor site, total number of fat grafting procedures, and processing technique.

Outcome Measures

The primary outcomes evaluated included local cancer recurrence with time to recurrence if applicable, and rate of distant metastasis. Surgical complications evaluated included infections requiring antibiotics and/or operative washout, hematoma, seroma, wound healing complications, capsular contracture, implant exposure, and flap failure. These complications were further subcategorized as minor or major (requiring operative intervention/surgical exploration or explantation).

Statistical Analysis

Data were imported into IBM SPSS Version 23.0 software (IBM Corp., Armonk, N.Y.) for analysis purposes. Statistical testing was performed, with values of $p < 0.05$ considered statistically significant by means of two-sided testing.

Patients were stratified dichotomously by whether they received autologous fat grafts. Breasts were further stratified by therapeutic versus prophylactic surgical indication. Numeric data were summarized by strata using mean ± SD, medians, and minimum to maximum range values. Numeric data were tested for mean equality between strata by means of independent samples *t* tests unless normality assumptions were invalid. Nonnormal data were tested for rank equality between strata by means of Mann-Whitney *U* tests. Categorical data were summarized using frequencies and percentages expressed per nonmissing data. Distributional equality between strata was assessed by means of Pearson chi-square tests or Fisher's exact tests depending on cell sample distribution. Post hoc Bonferroni adjusted *z* tests were performed in the presence of overall significance to assess proportional differences between strata for each subgroup.

Planned comparisons for demographic/patient characteristics, abnormality, treatment characteristics, and outcomes were supplemented with a post hoc investigation of those patients experiencing tumor recurrence. Patients were stratified by whether they experienced a tumor recurrence and similarly compared between strata to determine whether differences exist in demographics, pathologic condition, and/or treatment characteristics.

RESULTS

Demographics and Cancer History

The 248 fat-grafted breasts (162 therapeutic and 86 prophylactic) were compared to 581 controls (414 therapeutic and 167 prophylactic), which did not undergo fat grafting. The two groups were compared for differences in demographic factors. Overall, the autologous fat grafting and control groups represent well-matched groups. Between the therapeutic groups, patients who underwent fat grafting were significantly younger than control patients (47.8 ± 8.72 years versus 52.6 ± 11.1 years; $p < 0.001$). They were also less likely to have diabetes, hypertension, or hyperlipidemia (diabetes, 1.9 percent versus 8.0 percent, $p = 0.006$; hypertension, 16.0 percent versus 24.9 percent, $p = 0.022$; hyperlipidemia, 9.9 percent versus 20.0 percent, $p = 0.004$). There were no statistically significant differences in body mass index, smoking history, or history of other medical comorbidities including asthma, other nonbreast malignancy, depression, or hypothyroidism. There were also no significant differences between the autologous fat grafting prophylactic and control prophylactic groups (Table 1).

The two groups had similar cancer characteristics. When evaluated for *BRCA* status, the autologous fat grafting and non–autologous fat grafting groups had a statistically similar distribution of patients who were *BRCA*-negative (autologous fat grafting therapeutic, 89.1 percent, versus non–autologous fat grafting therapeutic, 89.0 percent; and autologous fat grafting prophylactic, 82.5 percent, versus non–autologous fat grafting prophylactic, 84.3 percent), *BRCA1*-positive (autologous fat grafting therapeutic, 6.4 percent, versus non–autologous fat grafting therapeutic, 3.5 percent; and autologous fat grafting prophylactic, 9.5 percent, versus non–autologous fat grafting prophylactic, 5.8 percent), and *BRCA2*-positive (autologous fat grafting therapeutic, 4.5 percent, versus non–autologous fat grafting therapeutic, 7.5 percent); and autologous fat grafting prophylactic, 7.9 percent, versus nonautologous fat grafting prophylactic, 9.9 percent). Furthermore, the two groups had similar Oncotype scores, with the majority of patients characterized as "low risk" (60.0 percent versus 62.8 percent) followed by "medium risk" (28.6 percent versus 31.0 percent)

Table 1. Patient Demographics

	No Fat Graft (n = 581)		Fat Graft (n = 248)		p	
	Therapeutic (%)	Prophylactic (%)	Therapeutic (%)	Prophylactic (%)	Therapeutic	Prophylactic
No.	414	167	162	86		
Age, yr					<0.001	0.451
Mean ± SD	52.6 ± 11.1	49.0 ± 10.3	47.8 ± 8.7	48.1 ± 8.6		
Median	51.3	48.8	46.7	48.3		
BMI, kg/m^2					0.119	0.518
Mean ± SD	26.0 ± 5.5	25.4 ± 5.2	25.3 ± 4.2	25.1 ± 3.6		
Median	25.1	24.4	24.5	24.7		
Smoking history					0.319	0.435
Prior	131 (31.6)	49 (29.3)	60 (37.0)	29 (33.7)		
None	270 (65.2)	111 (66.5)	95 (58.6)	51 (59.3)		
Current	13 (3.1)	7 (4.2)	7 (4.3)	6 (7.0)		
Characteristics						
Diabetes	33 (8.0)	4 (2.4)	3 (1.9)	1 (1.2)	0.006	0.664
Hypertension	103 (24.9)	26 (15.6)	26 (16.0)	11 (12.8)	0.022	0.554
Hyperlipidemia	83 (20.0)	28 (16.8)	16 (9.9)	9 (10.5)	0.004	0.179
Asthma	24 (5.8)	9 (5.4)	6 (3.7)	1 (1.2)	0.309	0.171
Anxiety	25 (6.0)	11 (6.6)	13 (8.0)	8 (9.3)	0.388	0.438
Nonbreast malignancy	27 (6.5)	12 (7.2)	11 (6.8)	6 (7.0)	0.907	0.951
Depression	28 (6.8)	8 (4.8)	11 (6.8)	8 (9.3)	0.991	0.163
Hypothyroid	51 (12.3)	19 (11.4)	18 (11.1)	11 (12.8)	0.688	0.742

BMI, body mass index.

and least commonly "high risk" (11.4 percent versus 6.2 percent). The two groups were also compared for differences in hormone receptor (estrogen receptor and progesterone receptor) and human epidermal growth factor receptor status, with no statistically significant differences identified between the two groups.

In addition, there was no statistically significant difference in disease laterality between the two groups (right breast disease autologous fat grafting, 39.5 percent, versus non–autologous fat grafting, 42.8 percent; left breast disease autologous fat grafting, 41.4 percent, versus nonautologous fat grafting, 40.1 percent; and bilateral breast disease autologous fat grafting, 19.1 percent, versus non–autologous fat grafting, 17.1 percent) (Table 2).

The autologous fat grafting group had a statistically significant greater number of patients with ductal carcinoma in situ compared with the non–autologous fat grafting groups (30.2 percent versus 18.8 percent), and similarly of lower cancer stage; however, there were no statistically significant differences in rates of lobular carcinoma in situ, invasive lobular carcinoma, or invasive ductal carcinoma between the two groups (Table 3).

Table 2. Patient *BRCA* Status, Hormone Receptor Status, and Oncotype Score

	Therapeutic		
	No Fat Graft (%)	Fat Graft (%)	p
No.	414	162	
BRCA status			0.313
Negative	202 (89.0)	98 (89.1)	
BRCA2	17 (7.5)	5 (4.5)	
BRCA1	8 (3.5)	7 (6.4)	
Oncotype score			0.586
Low risk	71 (62.8)	21 (60.0)	
Medium risk	35 (31.0)	10 (28.6)	
High risk	7 (6.2)	4 (11.4)	
Estrogen receptor			0.700
Negative	56 (13.7)	26 (16.3)	
Positive	337 (82.4)	127 (79.4)	
Unknown	16 (3.9)	7 (4.4)	
Progesterone receptor			0.901
Negative	84 (20.5)	35 (21.9)	
Positive	309 (75.6)	118 (73.8)	
Unknown	16 (3.9)	7 (4.4)	
HER status			0.568
Negative	267 (80.7)	87 (78.4)	
Positive	61 (18.4)	24 (21.6)	
Unknown	3 (0.9)	0	
Disease laterality			0.741
Right	177 (42.8)	64 (39.5)	
Left	166 (40.1)	67 (41.4)	
Bilateral	71 (17.1)	31 (19.1)	

HER, human epidermal growth factor receptor.

Medical Cancer Treatment

The autologous fat grafting and non–autologous fat grafting groups were compared for rates of chemotherapy and chemotherapy duration. Prophylactic breasts were also analyzed, as chemotherapy is a systemic treatment. The two groups demonstrated similar rates of chemotherapy administration (autologous fat grafting therapeutic, 43.2 percent, versus non–autologous fat grafting therapeutic, 50.7 percent); and autologous fat grafting prophylactic, 44.2 percent,

Table 3. Surgical Indication and Breast Cancer Stage

	Therapeutic		
	No Fat Graft (%)	Fat Graft (%)	*p*
No.	414	162	
Surgical indication			0.012
Mixed IDC and ILC	12 (2.9)	0	
LCIS	5 (1.2)	2 (1.2)	
ILC	49 (11.8)	15 (9.3)	
IDC	270 (65.2)	96 (59.3)	
DCIS	78 (18.8)	49 (30.2)	
Pathologic stage			0.024
3	39 (9.4)	10 (6.2)	
2	143 (34.5)	46 (28.4)	
1	149 (36.0)	55 (34.0)	
0	83 (20.0)	51 (31.5)	

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; DCIS, ductal carcinoma in situ.

versus non–autologous fat grafting prophylactic, 45.5 percent). In addition, there were similar rates of adjuvant and neoadjuvant chemotherapy between the two groups. Furthermore, similar rates of patients in both groups did not undergo chemotherapy treatment (autologous fat grafting therapeutic, 56.8 percent, versus non–autologous fat grafting therapeutic 49.3 percent; and autologous fat grafting prophylactic, 55.8 percent, versus non–autologous fat grafting prophylactic, 54.5 percent). Finally, the mean duration of chemotherapy treatment was similar in the two groups (autologous fat grafting therapeutic, 103.4 days, versus non–autologous fat grafting therapeutic, 102.4 days; and autologous fat grafting prophylactic, 111.5 days, versus non–autologous fat grafting prophylactic, 104.8 days).

When the two groups were compared for rates of hormone replacement therapy, the autologous fat grafting group had a statistically significant decreased rate of hormone replacement therapy compared with the non–autologous fat grafting group in both therapeutic (58.0 percent versus 69.3 percent; $p = 0.010$) and prophylactic (41.9 percent versus 62.9 percent; $p = 0.001$). Rates of immunotherapy, however, were similar between the two groups (autologous fat grafting therapeutic, 14.8 percent, versus non–autologous fat grafting therapeutic, 16.9 percent); and autologous fat grafting prophylactic, 14.0 percent, versus non–autologous fat grafting prophylactic, 13.2 percent). In addition, both groups underwent equal rates of radiation therapy (autologous fat grafting, 22.2 percent, versus non–autologous fat grafting, 22.2 percent) (Table 4).

Surgical Cancer Treatment

When the two groups were analyzed for differences in surgical treatment, patients in the autologous fat grafting group had higher rates of nipple-sparing mastectomy (autologous fat grafting therapeutic versus non–autologous fat grafting therapeutic, 33.3 percent versus 22.0 percent, respectively; autologous fat grafting prophylactic versus non–autologous fat grafting prophylactic, 36.0 percent versus 32.9 percent, respectively). The non–autologous fat grafting group demonstrated higher rates of total and skin-sparing mastectomy (autologous fat grafting therapeutic versus non–autologous fat grafting therapeutic, 60.5 percent versus 77.1 percent,

Table 4. Medical Therapy

	No Fat Graft (*n* = 581)		Fat Graft (*n* = 248)		*p*	
	Therapeutic (%)	Prophylactic (%)	Therapeutic (%)	Prophylactic (%)	Therapeutic	Prophylactic
No.	414	167	162	86		
Receiving chemotherapy					0.205	0.816
Adjuvant	168 (40.6)	58 (34.7)	53 (32.7)	27 (31.4)		
Neoadjuvant	42 (10.1)	18 (10.8)	17 (10.5)	11 (12.8)		
None	204 (49.3)	91 (54.5)	92 (56.8)	48 (55.8)		
Chemotherapy duration, days					0.832	0.262
Mean ± SD	102.4 ± 32.9	104.8 ± 31.3	103.4 ± 29.9	111.5 ± 25.7		
Median	102	102.5	105	105		
Receiving hormone therapy	287 (69.3)	105 (62.9)	94 (58.0)	36 (41.9)	0.010	0.001
Tamoxifen	163 (39.4)	74 (44.3)	73 (45.1)	28 (32.6)	0.212	0.071
Anastrozole	92 (22.2)	27 (16.2)	19 (11.7)	7 (8.1)	0.004	0.076
Letrozole	50 (12.1)	16 (9.6)	11 (6.8)	4 (4.7)	0.064	0.169
Exemestane	17 (4.1)	5 (3.0)	4 (2.5)	2 (2.3)	0.346	1.000
Zoladex	11 (2.7)	9 (5.4)	9 (5.6)	5 (5.8)	0.088	1.000
Raloxifene	2 (0.5)	0	1 (0.6)	1 (1.2)	1.000	0.340
Lupron	1 (0.2)	2 (1.2)	3 (1.9)	0	0.070	0.549
Receiving immunotherapy	70 (16.9)	22 (13.2)	24 (14.8)	12 (14.0)	0.541	0.863
Receiving radiation therapy	92 (22.2)	0	36 (22.2)	0	1.000	NA

NA, not applicable.

respectively; autologous fat grafting prophylactic versus non–autologous fat grafting prophylactic, 54.7 percent versus 67.1 percent, respectively) and axillary dissection (autologous fat grafting therapeutic versus non–autologous fat grafting therapeutic, 21.0 percent versus 31.9 percent, respectively); both were statistically significant (Fig. 1).

The two groups were also analyzed for differences in reconstruction modality. The majority of patients in both groups underwent tissue expander–to-implant reconstruction (autologous fat grafting therapeutic versus non–autologous fat grafting therapeutic, 59.9 percent versus 69.6 percent, respectively; and autologous fat grafting prophylactic versus nonautologous fat grafting prophylactic, 55.8 percent versus 66.5 percent, respectively). The second most common modality was autologous reconstruction (autologous fat grafting therapeutic versus non–autologous fat grafting therapeutic, 24.7 percent versus 15.0 percent, respectively; and autologous fat grafting prophylactic versus non–autologous fat grafting prophylactic, 26.7 percent versus 13.2 percent, respectively). Finally, a small minority of patients underwent immediate implant insertion (autologous fat grafting therapeutic versus nonautologous fat grafting therapeutic, 3.1 percent versus 12.1 percent, respectively; and autologous fat grafting prophylactic versus non–autologous fat grafting prophylactic, 3.1 percent versus 17.4 percent, respectively). When implant-based and autologous reconstructions were evaluated for frequency of autologous fat grafting, fat grafting more commonly occurred in breasts undergoing autologous reconstruction (24.6 percent fat grafting rate in implant-based reconstructions overall compared to 42.5 percent fat grafting rate in autologous reconstruction) (Fig. 2).

Fat grafting was performed using the Coleman technique and centrifugation. Fat grafting was performed at an average of 370.5 days (13.2 months) from initial breast reconstruction. Patients underwent an average of 1.23 fat grafting procedures, with a range of one to four procedures overall. The abdomen was the most common fat donor site; 70.2 percent of patients had fat harvested from the abdomen, followed by 41.5 percent from the flanks, 37.1 percent from the thighs, and 1.6 percent from the back (some patients had fat harvested from more than one donor site). The average volume of fat grafting was 109.4 cc.

Complications

Following fat grafting, the overall complication rate was 9.4 percent ($n = 22$). The most common complication was oil cyst formation (6.0 percent), followed by infection (1.7 percent) and fat necrosis (1.3 percent). One patient who underwent fat grafting also experienced wound healing complications (0.4 percent). No patients experienced hematoma or seroma following fat grafting procedures (Table 5).

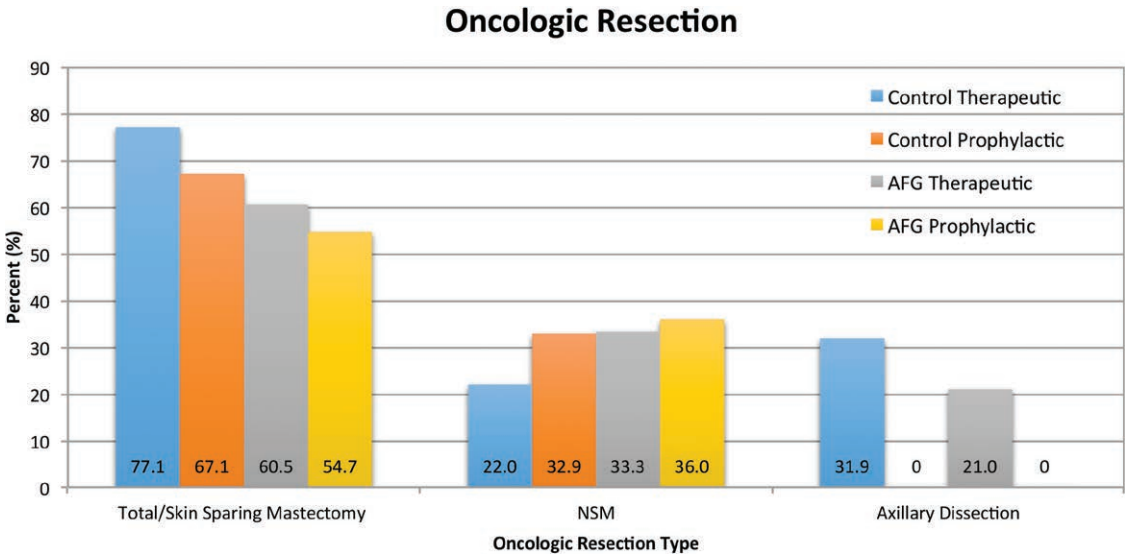

Fig. 1. Oncologic resection. Distribution of mastectomy, nipple-sparing mastectomy, and axillary dissection among patients by group (prophylactic versus therapeutic and autologous fat grafting versus control). Patients in the autologous fat grafting (*AFG*) group had higher rates of nipple-sparing mastectomy (*NSM*), whereas controls demonstrated higher rates of total and skin-sparing mastectomy and axillary dissection.

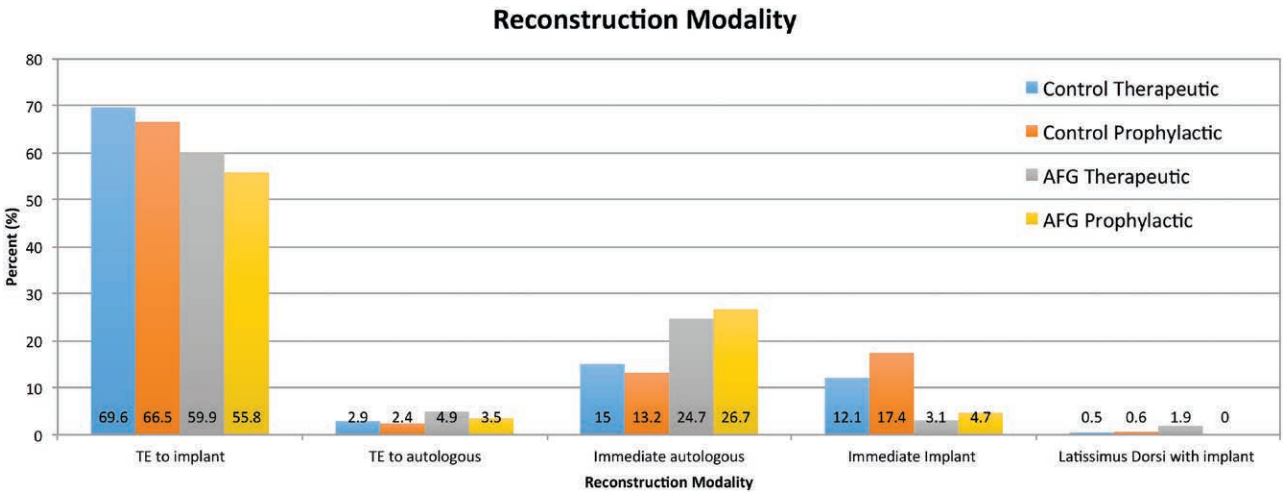

Fig. 2. Reconstruction modality. Distribution of reconstruction modalities among patients; the two groups were also analyzed for differences in reconstruction modality. The majority of patients in both groups underwent tissue expander–to-implant reconstruction with tissue expander (*TE*) followed by autologous reconstruction. *AFG*, autologous fat grafting.

Cancer Recurrence

Patients were followed for an average of 41.5 months (autologous fat grafting therapeutic group versus non–autologous fat grafting therapeutic group, 45.6 ± 20.4 months versus 38.8 ± 20.8 months, respectively; and autologous fat grafting prophylactic group versus nonautologous fat grafting prophylactic group, 42.5 ± 17.4 months versus 37.6 ± 20.0 months, respectively) from initial reconstruction.

Rates of local cancer recurrence were similar between the two groups, occurring in four breasts (2.5 percent) in the autologous fat grafting group and eight breasts (1.9 percent) in the non–autologous fat grafting group ($p = 0.747$). The average time to cancer recurrence appeared to be longer in the autologous fat grafting group, at 52.3 ± 15.2 months in the autologous fat grafting group versus 22.8 ± 11.8 months in the non–autologous fat grafting group; the difference was statistically significant ($p = 0.016$). Conversely, rates of distant metastasis were similar between the two groups, with three patients (1.9 percent) in the autologous fat grafting group developing distant metastasis versus 13 patients (3.1 percent) in the non–autologous fat grafting group. The mean time to metastasis occurrence was 38.6 months (range, 17.9 to 61.3 months) in the autologous fat grafting group and 29.2 months (range, 1.5 to 65.7 months) in the control group ($p = 0.482$). These metastases were identified in the brain, bone, lung, and liver (Table 6).

The two groups were evaluated for disease-free (or recurrence-free) interval. As depicted in Figure 3, the autologous fat grafting and non–autologous fat grafting curves are initially overlapping; however, the non–autologous fat grafting curve does fall below that of the autologous fat grafting curve at approximately 40 months. The tail discrepancy seen after 65 months is caused by censoring of controls; controls are not included past this point, because they were not followed after this point.

Table 5. Overall Autologous Fat Grafting Complications

	Fat Graft Patients (%)
No. of patients	234
Overall complications	22 (9.4)
Oil cyst	14 (6.0)
Infection	4 (1.7)
Major	2 (0.9)
Minor	2 (0.9)
Fat necrosis	3 (1.3)
Wound healing problems	1 (0.4)
Seroma	0 (0)
Hematoma	0 (0)

Analysis of Factors Predisposing to Cancer Recurrence

A multivariate analysis was performed to identify risk factors for locoregional and distant cancer recurrence. There were no patient demographic factors associated with increase in breast cancer recurrence. Interestingly, neither *BRCA* status, hormone receptor status, human epidermal growth factor *receptor* status, nor Oncotype score was associated with an increased rate of cancer recurrence.

Table 6. Locoregional Recurrence and Distant Breast Cancer Metastasis

	No Fat Graft (n = 581)		Fat Graft (n = 248)		p	
	Therapeutic (%)	Prophylactic (%)	Therapeutic (%)	Prophylactic (%)	Therapeutic	Prophylactic
No.	414	167	162	86		
Local recurrence	8 (1.9)	0	4 (2.5)	0	0.747	NA
Time to recurrence, mo					0.016	NA
Mean ± SD	22.8 ± 11.84	NA	52.3 ± 15.18	NA		
Median	19.1	NA	54.9	NA		
Distant metastasis	13 (3.1)	0	3 (1.9)	0	0.575	NA

NA, not applicable.

As expected, invasive breast cancer was a risk factor for subsequent recurrence compared to breasts that were treated prophylactically; 8.3 percent of breasts that recurred were diagnosed with invasive ductal or lobular cancer. However, pathologic stage was not associated with increase in breast cancer recurrence rates.

When treatment modalities were analyzed, patients with recurrence were more likely to have received neoadjuvant chemotherapy and radiation therapy than those that without recurrence (41.7 percent versus 10.2 percent and 50 percent versus 14.9 percent, respectively; $p < 0.05$). Nevertheless, there were no statistically significant increases in cancer recurrence in patients receiving immunotherapy or hormone therapy.

Although mastectomy type was not different among breasts with recurrence and no recurrence, patients who required axillary node dissection were more likely to experience cancer recurrence. Finally, plastic surgery reconstruction modality did not affect overall recurrence (Table 7).

DISCUSSION

In 1987, the American Society of Plastic Surgeons banned autologous fat grafting to breasts over concern for future cancer surveillance in the setting of fat necrosis.[15] In 2007, the American Society of Plastic Surgeons established a task force to reevaluate the potential hazards and benefits of fat grafting and concluded that radiographic technology could distinguish grafted

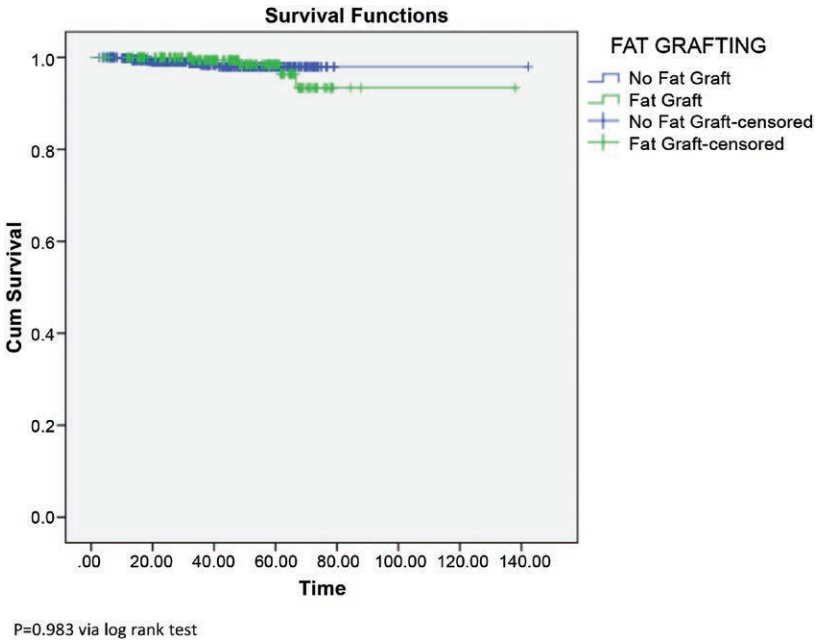

Fig. 3. Kaplan-Meier curve of disease-free interval. Up to 65 months, the two disease-free interval curves are overlapping. The tail discrepancy (after 65 months) is caused by censoring of the non–autologous fat grafting group, which was not included because they were not followed after that point.

Table 7. Significant Contributors to Breast Cancer Recurrence

	No Recurrence (%)	Recurrence (%)	*p*
Invasive pathologic condition	11 (1.3)	1 (8.3)	0.041
Neoadjuvant chemotherapy	83 (10.2)	5 (41.7)	0.012
Radiation therapy	122 (14.9)	6 (50.0)	0.005
Axillary dissection	161 (19.7)	6 (50.0)	0.020

fat from potentially dangerous lesions.[5] Subsequently, the ban on fat grafting was lifted in 2009 by the American Society of Plastic Surgeons Fat Graft Task Force, which determined from a limited number of studies that there appeared to be no interference with breast cancer detection.[16] Since 2009, several studies have investigated the oncologic safety of fat grafting with conflicting results, including a recent study published by Kronowitz et al., evaluating the oncologic safety of autologous fat grafting using a control group for comparison.[14] Given the equivocal nature of previous studies evaluating the oncologic safety of autologous fat grafting, and in light of its widespread use, we feel that further investigation on this topic is warranted. Our study differs from that of Kronowitz et al. in that we specifically evaluated patients who underwent total mastectomy and breast reconstruction with autologous fat grafting, excluding those who underwent lumpectomy or partial mastectomy. We feel that lumpectomy patients are a unique subset of patients undergoing breast reconstruction; postoperatively, they maintain breast tissue, which may impact breast cancer recurrence rates. This set of data is being evaluated by our group separately.

Here, we present data on a large number of fat-grafted breasts evaluating both local/distant cancer recurrence and surgical outcomes. We demonstrate that autologous fat grafting does not increase risks of local or distant cancer recurrence or affect postoperative complication rates.

Our two study groups represent similar demographic and oncologic characteristics. In addition, *BRCA* status, Oncotype score, and hormone receptor status were similar between the two groups.

Although hormone receptor status was similar between the two groups, patients in the autologous fat grafting group were significantly less likely to receive hormone therapy. This was the result of decisions between the patient and the medical oncologist; plastic surgeons did not influence this treatment decision. This is particularly interesting in light of a study by Kronowitz et al., which found that hormonal therapy was associated with local tumor recurrence after autologous fat grafting, where the locoregional recurrence rate was three times that of controls.[17] Our study found no association between hormone therapy and tumor recurrence.

Although the two groups displayed no differences in treatment with chemotherapy, hormone therapy, or immunotherapy, they did demonstrate differences in surgical management. Patients who underwent autologous fat grafting were more likely to have undergone nipple-sparing mastectomy without axillary lymph node dissection, in contrast to the non–autologous fat grafting group, where total/skin-sparing mastectomy in conjunction with axillary dissection was more common. When compared for reconstructive modalities, autologous fat grafting occurred more common in breasts that underwent autologous reconstruction and less commonly in breasts that underwent implant-based reconstruction.

Although autologous fat grafting is frequently used as a reconstructive adjunct in implant-based reconstruction, we found higher rates of autologous fat grafting in patients undergoing autologous reconstruction. We hypothesize that in the lower body mass index autologous group with autologous fat grafting, the patients desired increased volume and/or projection of the reconstructed breasts; and in the higher body mass index autologous group with autologous fat grafting, the patients desired an increase in breast size and the added benefit of abdominal contouring of liposuction. In the implant autologous fat grafting group, perhaps the need for fat grafting has decreased with more choices in silicone implant types, including anatomically shaped implants and highly cohesive implants. Our analysis of post–fat grafting complications demonstrates low complication rates, confirming existing data on its safety as a reconstructive adjunct.

Interestingly, patients who underwent autologous fat grafting developed local cancer recurrence in a delayed fashion (44.5 months versus 38.4 months). One study found that there are differences in gene expression among adipose cells adjacent to invasive breast tumors, adipose cells in breasts without malignant disease, and adipose cells distant from invasive breast tumors. It

may take time for the newly grafted adipose tissue, taken from a distant donor site, to shift into a molecular profile that is favorable to tumor growth, which is then reflected as a delay in cancer recurrence.[18]

In addition, the delay in detection of cancer recurrence in patients who underwent autologous fat grafting could possibly represent a delay in tumor detection secondary to interference with tumor detection, hypothesized by previous investigators. Although it follows that cancer recurrence would be detected later as more advanced disease in the autologous fat grafting group, this was not observed in our study. In addition, there was no increase in rates of distant metastasis in our autologous fat grafting group, with a distant metastasis rate of 1.9 percent in autologous fat grafting group compared with 3 percent in the control group.

Patients who did not undergo autologous fat grafting were more likely to have advanced disease based on pathologic cancer staging compared with patients who underwent autologous fat grafting. It follows that our autologous fat grafting group was more likely to have less advanced disease, with an increased incidence of ductal carcinoma in situ and lower stage, in conjunction with increased frequency of nipple-sparing mastectomy and decreased necessity for axillary dissection. This difference may play a role in the shorter time to cancer recurrence we observed in the non–autologous fat grafting group. However, our analysis determined that more advanced pathologic stage was not associated with increased breast cancer recurrence rates.

Our rate of local cancer recurrence in association with autologous fat grafting falls in line with existing reports; a review of 16 clinical studies including 2100 patients revealed a recurrence rate of 2.2 percent.[14,17] Furthermore, this rate of locoregional recurrence is similar to breast cancer recurrence in the general population of patients that do not undergo lipofilling, which is quoted at 1 to 2 percent per year.[19]

Although our findings suggest that neither the total volume of fat injected nor the total number of fat grafting sessions performed impacted locoregional recurrence, further studies are necessary to determine whether such a relationship exists given the inherent limitation of our retrospective study design. Despite this, our data do demonstrate that patients of similar demographics, cancer characteristics, and surgical outcomes who have undergone autologous fat grafting experience similar rates of postoperative complications with similar rates of local recurrence and distant metastasis, with a mean time to recurrence significantly longer in the autologous fat grafting group.

CONCLUSIONS

Autologous fat grafting is a powerful tool in breast reconstruction. This large single-institution study, which evaluates patients of comparable *BRCA* status, cancer staging, chemotherapy, and radiation therapy, provides valuable evidence-based support for its oncologic safety.

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REFERENCES

1. Claro F Jr, Figueiredo JC, Zampar AG, et al. Applicability and safety of autologous fat grafting to healthy breast tissue: A systematic review. *J Plast Reconstr Aesthet Surg.* 2014;67:437–448.
2. Largo RD, Tchang LA, Mele V, et al. Efficacy, safety and complications of autologous fat grafting to healthy breast tissue: A systematic review. *J Plast Reconstr Aesthet Surg.* 2014;67:437–448.
3. Mojallal A, Saint-Cyr M, Garrido I. Autologous fat transfer: Controversies and current indications for breast surgery. *J Plast Reconstr Aesthet Surg.* 2009;62:708–710.
4. Ke CC, Liu RS, Suetsugu A, et al. In vivo fluorescence imaging reveals the promotion of mammary tumorigenesis by mesenchymal stromal cells. *PLoS One* 2013;8:e69658.
5. Gutowski KA; ASPS Fat Graft Task Force. Current applications and safety of autologous fat grafts: A report of the ASPS fat graft task force. *Plast Reconstr Surg.* 2009;124:272–280.
6. Petit JY, Rietjens M, Botteri E, et al. Evaluation of fat grafting safety in patients with intraepithelial neoplasia: A matched-cohort study. *Ann Oncol.* 2013;24:1479–1484.
7. Agha RA, Fowler AJ, Herlin C, Goodacre TE, Orgill DP. Use of autologous fat grafting for breast reconstruction: A systematic review with meta-analysis of oncological outcomes. *J Plast Reconstr Aesthet Surg.* 2015;68:143–161.
8. Masia J, Bordoni D, Pons G, Liuzza C, Castagnetti F, Falco G. Oncological safety of breast cancer patients undergoing free-flap reconstruction and lipofilling. *Eur J Surg Oncol.* 2015;41:612–616.
9. Brenelli F, Rietjens M, De Lorenzi F, et al. Oncological safety of autologous fat grafting after breast conservative treatment: A prospective evaluation. *Breast J.* 2014;20:159–165.
10. Smit JM, Tielemans HJ, de Vries B, Tuinder SM. Recurrence of invasive ductal breast carcinoma 10 months after autologous fat grafting. *J Plast Reconstr Aesthet Surg.* 2014;67:e127–e128.
11. Schweizer R, Tsuji W, Gorantla VS, Marra KG, Rubin JP, Plock JA. The role of adipose-derived stem cells in breast cancer progression and metastasis (Review). *Stem Cells Int.* 2015;2015:120949.
12. Pearl RA, Leedham SJ, Pacifico MD. The safety of autologous fat transfer in breast cancer: Lessons from stem cell biology. *J Plast Reconstr Aesthet Surg.* 2012;65:283–288.
13. Silva-Vergara C, Fontdevila J, Descarrega J, Burdio F, Yoon TS, Grande L. Oncological outcomes of lipofilling breast reconstruction: 195 consecutive cases and literature review. *J Plast Reconstr Aesthet Surg.* 2016;69:475–481.

14. Kronowitz SJ, Mandujano CC, Liu J, et al. Lipofilling of the breast does not increase the risk of recurrence of breast cancer: A matched controlled study. *Plast Reconstr Surg.* 2016;137:385–393.
15. Report on autologous fat transplantation. ASPRS Ad-Hoc Committee on New Procedures, September 30, 1987. *Plast Surg Nurs.* 1987;7:140–141.
16. American Society of Plastic Surgeons. Fat transfer/fat graft and fat injection: ASPS guiding principles. Available at: http://www.plasticsurgery.org/Documents/medical-professionals/health-policy/guiding-principles/ASPS-Fat-Transfer-Graft-Guiding-Principles.pdf. Accessed October 14, 2016.
17. Charvet HJ, Orbay H, Wong MS, Sahar DE. The oncologic safety of breast fat grafting and contradictions between basic science and clinical studies: A systematic review of the recent literature. *Ann Plast Surg.* 2015;75:471–479.
18. Sturtz LA, Deyarmin B, van Laar R, Yarina W, Shriver CD, Ellsworth RE. Gene expression differences in adipose tissue associated with breast tumorigenesis. *Adipocyte* 2014;3:107–114.
19. Cao JQ, Olson RA, Tyldesley SK. Comparison of recurrence and survival rates after breast-conserving therapy and mastectomy in young women with breast cancer. *Curr Oncol.* 2013;20:e593–e601.