Treating Breast Conservation Therapy Defects with Brava and Fat Grafting: Technique, Outcomes, and Safety Profile

Michael N. Mirzabeigi, M.D.
Michael Lanni, B.S.
Catherine S. Chang, M.D.
Ran Y. Stark, M.D.
Stephen J. Kovach, M.D.
Liza C. Wu, M.D.
Joseph M. Serletti, M.D.
Louis P. Bucky, M.D.

Philadelphia, Pa.

Background: Fat grafting has been demonstrated as a means of reconstructing breast conservation therapy defects. However, there is continued uncertainty regarding its clinical efficacy and oncologic safety. Furthermore, the role of external preexpansion (i.e., with the Brava device) remains unclear in this setting. The purpose of this study was to examine the safety and clinical outcomes of Brava/fat grafting following breast conservation therapy.
Methods: A retrospective chart review was performed on all patients undergoing fat grafting following breast conservation therapy. Complications were defined as either a clinically palpable oil cyst/area of fat necrosis or infection. The mean time of follow-up was 2.3 years.
Results: A total of 27 fat grafting sessions were performed on 20 patients, with an overall complication rate of 25 percent. The mean interval from completion of radiation therapy to fat grafting was 7 years and was not a significant predictor for complications ($p = 0.46$). Among those who underwent repeated grafting, there was no difference in the complication rates between their first and second encounters ($p = 0.56$). There was no difference in complication rates between patients with Brava preexpansion and those without preexpansion. Patients undergoing Brava preexpansion had a significantly higher initial fill volume in comparison with those who did not (219 cc versus 51 cc; $p = 0.0017$). There were no cases of locoregional cancer recurrence following fat grafting.
Conclusion: Brava preexpansion was associated with higher initial fill volume in the setting of breast conservation therapy defects. (*Plast. Reconstr. Surg.* 140: 372e, 2017.)

Breast conservation therapy is a common alternative to mastectomy for early-stage breast tumors. Breast conservation therapy combines local excision and radiation therapy, which obviates the need to remove the entire breast; however, the resultant defect is often deforming nonetheless. Traditional means of breast reconstruction are generally ill-suited for reconstructing a partial breast defect.

The use of fat grafting to reconstruct breast conservation therapy defects stands as a burgeoning paradigm.[1] Lipofilling provides an autologous reconstructive modality, results in minimal donor-site morbidity, and does not expend traditional donor sites in the event of an eventual mastectomy.[2,3] Despite the growing acceptance, much uncertainty remains regarding both the aesthetic outcomes and oncologic implications of fat grafting for breast conservation therapy defects. The paradox of transferring an avascular graft to an unfavorable (scarred and radiated) recipient site and the expectation for transplanted fat to also be regenerative has led to debate regarding clinical efficacy and oncologic safety.

Further clouding this debate, there are limited clinical data to guide preexpansion with an external negative-pressure system (Brava LLC, Miami,

From the Division of Plastic Surgery, University of Pennsylvania Health System.
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Fla.) in the setting of lumpectomy defects. In the absence of level III (or greater) data, it is a matter of conjecture as to whether the affected breast conservation therapy breast tissue will preexpand to increase the recipient volume as has been demonstrated in native, healthy breast tissue. In addition, residual oncologic concerns surrounding fat grafting breast conservation therapy defects are heightened with the addition of Brava, as applied negative pressure alone may induce proliferative/angiogenic change. Therefore, the purpose of this study was to examine the techniques, clinical outcomes, and oncologic safety of combining Brava along with fat grafting to reconstruct breast conservation therapy defects.

PATIENTS AND METHODS

A retrospective review of records was performed on all patients who underwent breast conservation therapy with subsequent fat grafting to the ipsilateral breast at the Division of Plastic Surgery, University of Pennsylvania, from July of 2009 to March of 2015. Institutional review board approval was granted for this study.

A shared electronic medical record system included information obtained from office visits to medical oncologists, surgical oncologists, radiation oncologists, and plastic surgeons. Multidisciplinary records were used to identify the timing and details of the patient's course of breast conservation therapy. This information included patient demographics, comorbidities, timing of oncologic resection, and timing of radiation therapy. Hospital and outpatient records were used to determine perioperative factors, which included the use of Brava and the volume of fat grafted to each breast. Routine postoperative office visits included a detailed physical examination that was well-documented among all attending surgeons. According to institutional protocol, patients were instructed to return for outpatient follow-up at 2 weeks postoperatively and typically undergo a second physical examination within 6 months of fat grafting. Long-term cancer recurrence data were obtained from radiographic surveillance results and outpatient oncology records. Complications were calculated per breast and defined as either a clinically palpable oil cyst/area of fat necrosis or infection. Patients with inadequate long-term follow-up were excluded from the analysis of complications.

Statistical Analysis

Data were deidentified and entered into Stata/IC 13.1 (StataCorp, College Station, Texas) for analysis. Descriptive statistics were computed for the study population including mean (interquartile range) for continuous data and frequency (percentage) for categorical data. Shapiro-Wilk results were used to guide testing decisions. Categorical variables were analyzed by means of Fisher's exact test (or chi-square test when appropriate). Continuous variables were analyzed using the Wilcoxon-Mann-Whitney test or simple logistic regression. Comparisons between initial and repeated grafting used the McNemar test. Factors found to be significant in the bivariate analyses were included in a multiple regression model to identify predictors of increasing fill volume. All tests were two-sided, and a value of $p \leq 0.05$ was used to determine statistical significance.

Brava Patient Selection and Protocol

There were two factors that dictated whether patients did or did not undergo Brava preexpansion before fat grafting. The first factor was attending physician preference. Although other surgeons included in this study use Brava for aesthetic augmentation, only the senior author (L.P.B.) routinely offers preoperative Brava external expansion in the setting of lumpectomy defects (Figs. 1 through 4).

The second factor was patient preference. Patients are counseled extensively regarding the need for daily compliance with the device and are given time with the device in the office. If patients anticipate marked disruption of their personal/professional routine or generalized device intolerance, fat grafting is planned without preexpansion.

Patients in the Brava cohort underwent external expansion for 5 weeks before undergoing fat grafting. Interval training was used to progressively increase the frequency and intensity of the external preexpansion. Of note, the 5-week protocol is longer than the typical 3-week protocol that the senior author uses for fat grafting in the setting of aesthetic breast augmentation.

Fat Grafting Technique

Fat grafting was performed by the respective attending surgeon. The fat processing technique varied based on the volume of lipoaspirate required. Low-volume fat grafting cases were defined as less than 100 cc of grafted lipoaspirate. Lipoaspirate in these cases was harvested by hand-held 10-cc syringes and a single-hole

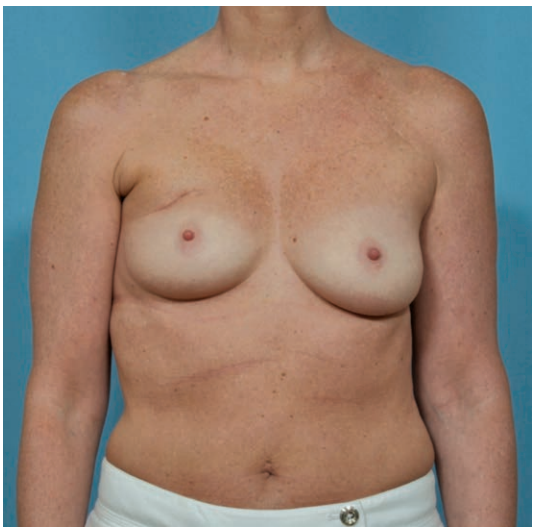

Fig. 1. Anteroposterior view of patient with a breast conservation therapy defect before fat grafting.

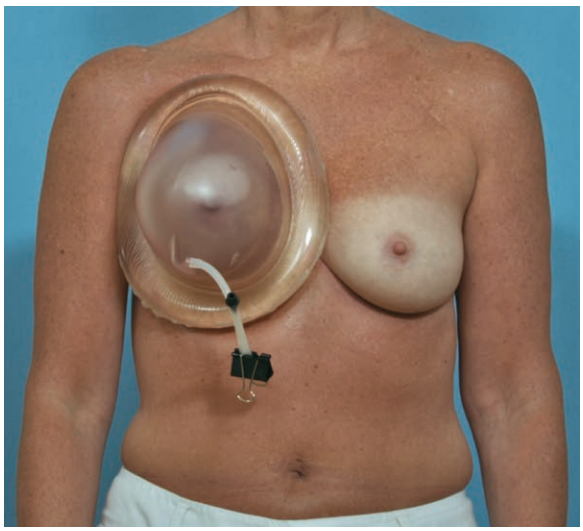

Fig. 3. Brava applied to ipsilateral breast for 5 weeks.

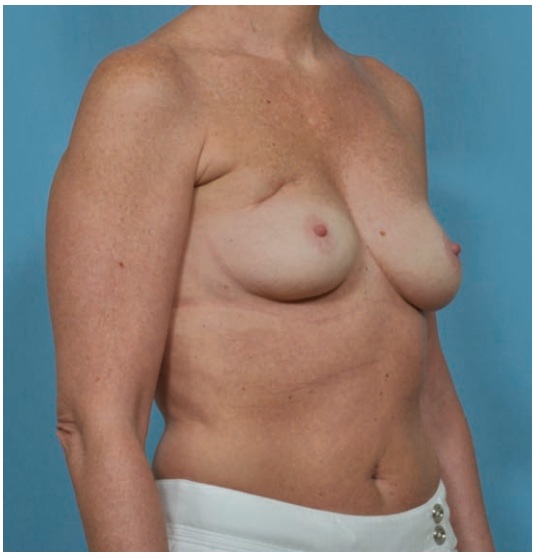

Fig. 2. Three-quarters view of a patient with a breast conservation therapy defect before fat grafting.

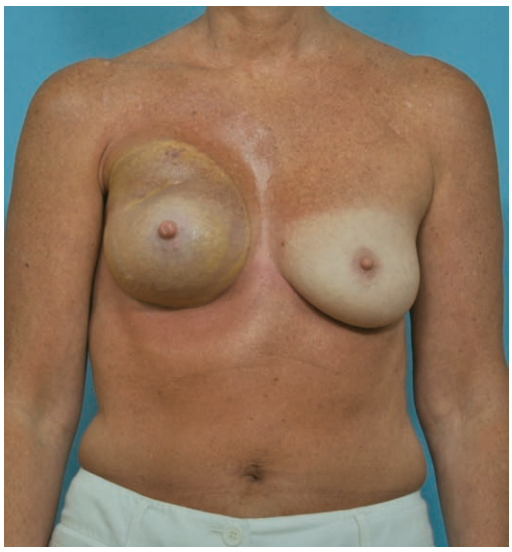

Fig. 4. Hyperemic, edematous change after 5 weeks of Brava preexpansion but before fat grafting.

4-mm cannula. Lipoaspirate in the remainder of cases was harvested using high-volume fat grafting technique, which included a multihole cannula on continuous suction of −750 mmHg. The lipoaspirate was collected in a sterile canister and distributed to 60-cc syringes for 2 minutes of low-force, hand-crank centrifugation (20 to 40 *g*). The postcentrifugation lipoaspirate was then injected from the 60-cc syringe through a 4-mm, single-hole cannula.

Lipotumescence and Needle Band Release

Defects were injected with approximately 75 percent of the ultimate fill volume. Using the concept of lipotumescence,[1] the initial volume injected allows scar bands to be placed under tension to facilitate percutaneous release. The irregularities or areas resistant to filling allow the surgeon to visualize where to release, and again, place the area under tension. A single hook can be used for additional countertraction on tethered tissue and a 14-gauge needle is used for percutaneous release. The senior author prefers fewer percutaneous insertions and favors multidirectional passes with the 14-gauge needle when in the subdermal plane (Figs. 5 and 6). Once the tissue is fully released, the remainder of the fat (i.e., the remaining 25 percent) was injected. The authors believe that the endpoints are rather

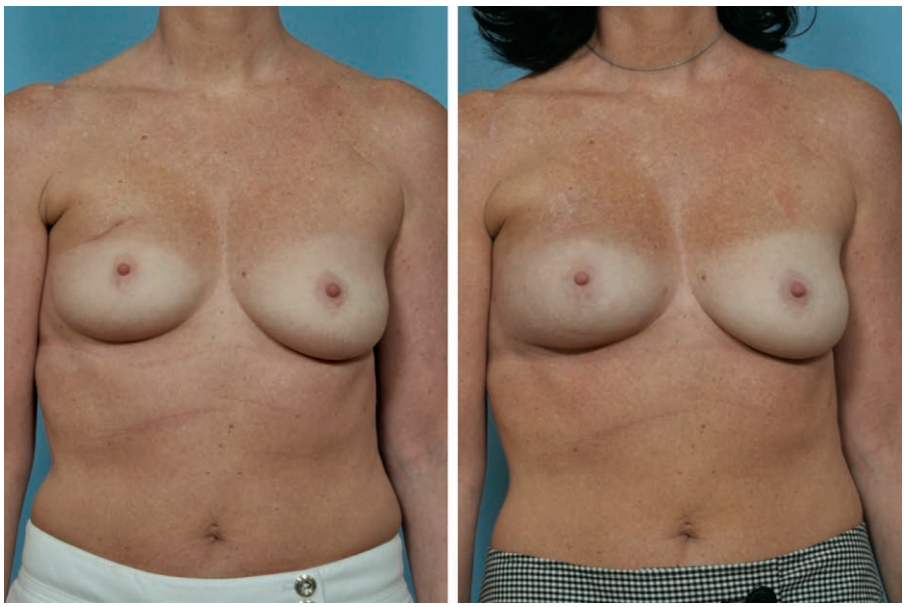

Fig. 5. Postoperative result following fat grafting.

objective and consistent among the attending surgeons. Fat injection to the defect is stopped based on the presence of tissue blanching, recession of fat from entry sites, and inability to place more aliquots of fat without excessive pressure on the syringe.

RESULTS

A total of 27 fat grafting sessions were performed on 20 patients, with an overall complication rate of 25 percent (Table 1). Of the 27 sessions, nine (33 percent) were performed with Brava preexpansion. Donor sites included the trunk (abdomen, flanks), the lower extremity, or a combination of both. There was no association between complications and the donor-site location ($p = 0.94$). The mean interval from completion of radiation therapy to fat grafting was 7 years and was not a significant predictor for complications ($p = 0.46$). Descriptive statistics of the subject population and univariate analysis are detailed in Table 1. Of note, there was no association between complications and patient age ($p = 0.26$) or body mass index ($p = 0.70$).

There were five cases of repeated grafting to the same defect. There was no significant difference between the mean volume of the initial session versus the repeated encounter. Among those who underwent repeated grafting, there was no difference in the complication rates between their first and second encounters ($p = 0.56$), with a mean time interval of 7 months between grafts.

Brava/Fill Volumes

There was no difference in complication rates between patients with Brava preexpansion and those without preexpansion (Table 2). Patients undergoing Brava preexpansion had a significantly higher initial fill volume compared with those who did not (219 cc versus 51 cc; $p = 0.0017$). Overall, greater fill volumes were not associated with a higher rate of complications ($p = 0.261$). Comparing the fill volumes across various subgroups in a bivariate analysis revealed that significantly larger fill volumes were associated with Brava use, age younger than 50 years, and over 5 years since the most recent radiation therapy (Fig. 7). A multiple regression model ($F = 15.6$, $p = 0.0001$) revealed that Brava was a significant predictor of increasing fill volumes (Table 3).

Cancer Recurrence

There were no cases of locoregional cancer recurrence following fat grafting, with a mean follow-up time of 2.3 years.

DISCUSSION

Over the past 10 years, fat grafting to the breast has reemerged from the historical footnotes of the plastic surgery literature to become a cornerstone of aesthetic and reconstructive breast surgery.[4] Coleman's landmark study in 2007 is largely credited with reviving the once dismissed notion of safely fat grafting the breast.[5] After the publication of Coleman's work, Khouri

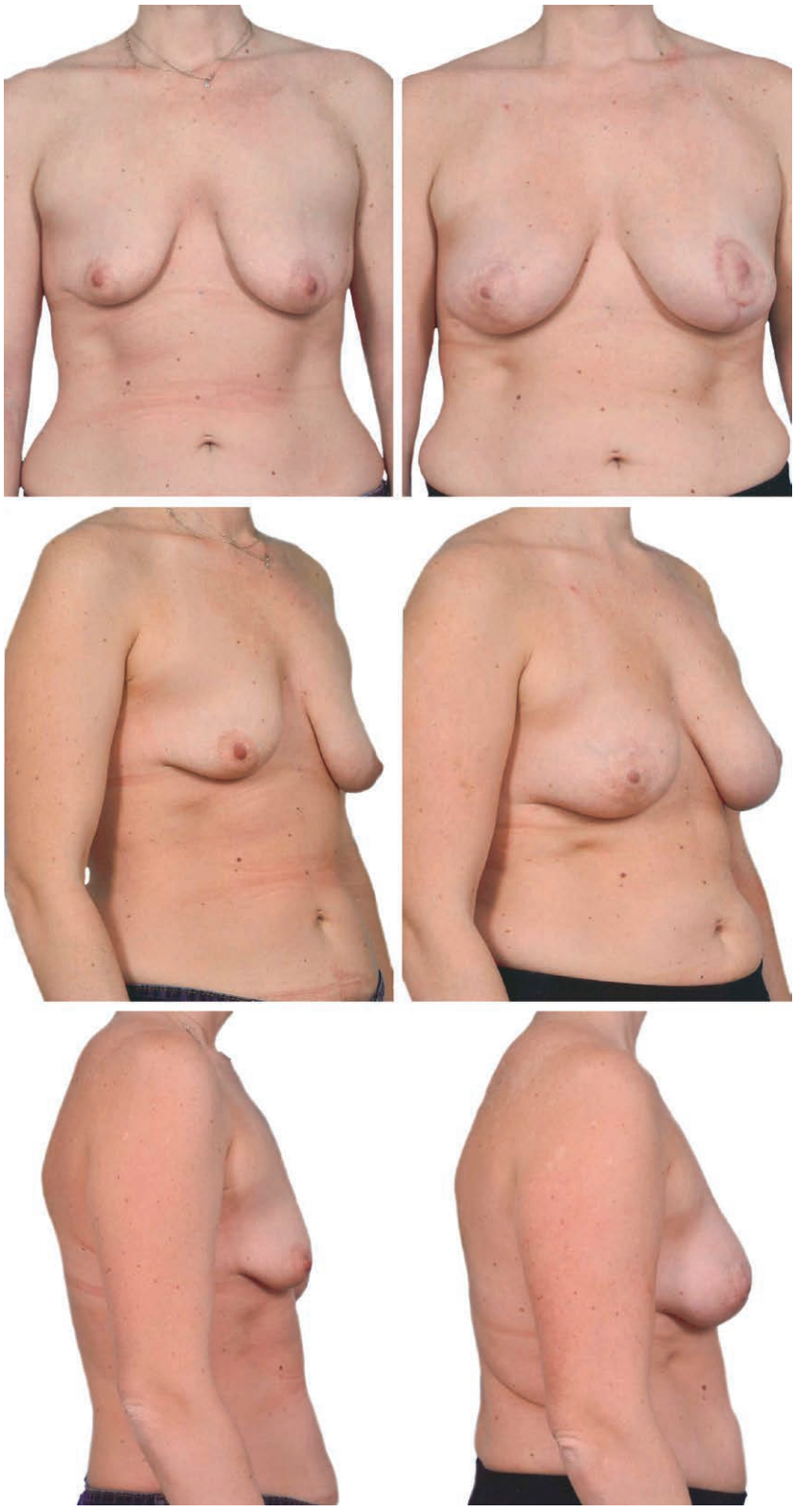

Fig. 6. (*Above*) Anteroposterior preoperative and postoperative views of a patient with breast conservation therapy defect. The patient was treated with fat grafting to the ipsilateral breast and subsequently underwent contralateral fat grafting. (*Center*) Oblique views of the patient preoperatively and postoperatively. (*Below*) Lateral views of the patient preoperatively and postoperatively.

Table 1. Complications and Management

Patient	Complication	Management
Repeated graft in 48-yr-old woman	Fat necrosis	Needle aspiration
Initial graft in 47-yr-old woman	Fat necrosis	Managed conservatively
Initial graft in 49-yr-old woman	Fat necrosis	Managed conservatively
Initial graft in 65-yr-old woman	Oil cyst	Aspirated intraoperatively
Initial graft in 30-yr-old woman	Dystrophic calcification	Managed conservatively
Initial graft in 55-yr-old woman	Fat necrosis and infection	Fat necrosis excised during revision

Table 2. Analysis of Perioperative Variables Comparing Complicated and Uncomplicated Cases of Fat Grafting Breast Conservation Therapy Defects*

	No Complication (%)	Complication (%)	*p*
Total no.	18 (75)	6 (25)	
Age, yr			
Mean	54.4	49	
Range	48–64	47–55	0.26
BMI, kg/m^2			
Mean	25.0	25.6	
Range	22.5–27.4	23.7–26.5	0.70
Donor site			0.94
Trunk	11 (78.6)	3 (21.4)	
LE	5 (71.4)	2 (28.6)	
Trunk and LE	3 (75)	1 (25)	
Fill volume, cc			
Mean	96.6	157.5	
Range	27–157.5	80–265	0.261
Brava preexpansion	6 (33.3)	3 (50)	0.34
Brava fill volume, cc			
Mean	207.4	245	
Range	165–300	115–355	0.65
No Brava fill volume, cc			
Mean	46.3	70	
Range	24–50	50–80	0.072
Years since last radiation therapy			
Mean	6.94	7	
Range	2–9	5–10	0.46
Repeated grafting			
Required second graft	3 (33.3)	2 (66.7)	0.55
Months between grafts			
Mean	4.7	7	
Range	4–5	5–10	0.16

BMI, body mass index; LE, lower extremity.
*Note that the total number of sessions is 24, as 3 were excluded from the univariate analysis because of inadequate follow-up.

has since published a series of sentinel studies that have contributed immeasurably to the scientific and clinical foundation of fat grafting. Interwoven in the work of Khouri et al. has been the study and application of external negative-pressure expansion (delivered by the Brava device).[6–10]

Brava in Irradiated Fields

Brava was initially described as a standalone method to increase tissue volume in aesthetic breast augmentation.[11] Given the modest effects of Brava as a singular modality, Brava was eventually repurposed as a pretreatment to increase recipient volume before fat grafting. External negative pressure increases the volume of the vascularized soft-tissue envelope through multiple physiologic pathways including but not limited to increased mechanical strain, adipogenic prolonged edema, and intermittent local ischemia.[12,13] Outcomes studies in aesthetic augmentation have since validated Brava as an effective means of increasing fill volume and therefore reduce the number of fat grafting sessions required to achieve a desired outcome. The efficacy of Brava in treating an irradiated tissue envelope and the ability to increase irradiated soft-tissue volume by using Brava remains unclear.

Prior studies have suggested that radiation therapy might be a contraindication to Brava/fat grafting, citing device intolerance

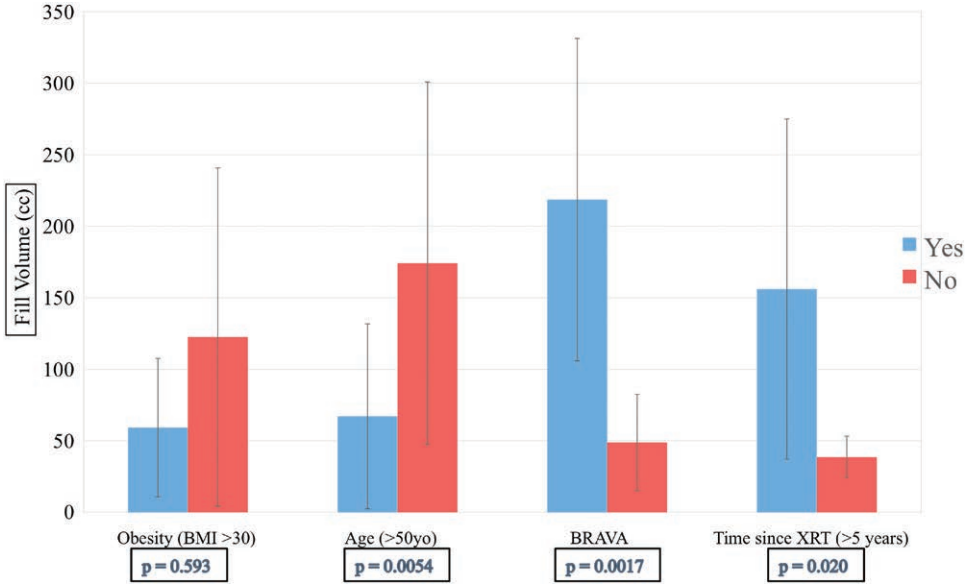

Fig. 7. Fill volume and associated factors on univariate analysis. *BMI*, body mass index; *XRT*, radiation therapy.

Table 3. Multivariate Regression of Factors Associated with Increased Fill Volume

Factor	Coefficient (95% CI)	*p*
Age <50 yr	−14.7 (−91 to 61)	0.69
Brava	174.7 (91 to 259)	<0.001
XRT >5 yr ago	27.6 (−48 to 103)	0.0078

XRT, radiation therapy.

(device-related dermatitis/skin complications) and high complication rates.[14] Although prior studies have described fat grafting lumpectomy defects, this is the first study to directly compare fat grafting lumpectomy defects with and without Brava; thus, the data provided herein are novel level III evidence suggesting an increase in fill volume with Brava (i.e., the irradiated envelope will expand) while maintaining a reasonable complication profile. The Brava cohort demonstrated a mean fill volume that was over four times higher (219 cc versus 51 cc), and Brava pretreatment was identified as a factor associated with higher fill volumes on multivariate analysis ($p < 0.0001$). These data suggest that Brava does increase the recipient volume of the lumpectomy site as has been similarly demonstrated in healthy breast tissue. Obviously, fill volume is an imperfect, multifactorial, and surgeon-dependent metric for evaluating the efficacy of Brava. Therefore, one must also examine complication rates to ensure that the higher fill volume is not simply observed following overzealous grafting in the Brava cohort.

Complication Rate

The overall complication rate was 25 percent in this series. In comparison, the incipient series of Brava/fat grafting published by the senior author demonstrated zero complications (confirmed by magnetic resonance imaging at 6 months) in native, healthy breast tissue.[15] Although there has been speculation that fat (and/or the associated stromal vascular fraction of lipoaspirate) has regenerative properties,[16–20] fat remains an avascular graft dependent on the quality of the recipient site. Breast conservation therapy's combination of surgical scar and prior radiation therapy creates a hostile recipient site. The unfavorable recipient site yields a higher complication rate regardless of fat processing method or meticulous delivery technique. In the largest series of fat grafted lumpectomy defects to date (91 cases), Khouri et al. describe rates of palpable masses to be notably higher in irradiated fields.

Complication rates are, however, dependent on the graft-to-capacity ratio as described by Del Vecchio and Del Vecchio.[21] It is the authors' belief that the microvascular damage and soft-tissue fibrosis caused by breast conservation therapy results in a "left shift" in the graft-to-capacity ratio (Fig. 8). This means that volume maintenance will be lower (and complications will be higher) for breast conservation therapy patients in comparison with cases involving healthy breast tissue. Brava likely does not "shift" or normalize the curve, as it may not reverse radiation-induced microvascular damage to a clinically significant degree. This

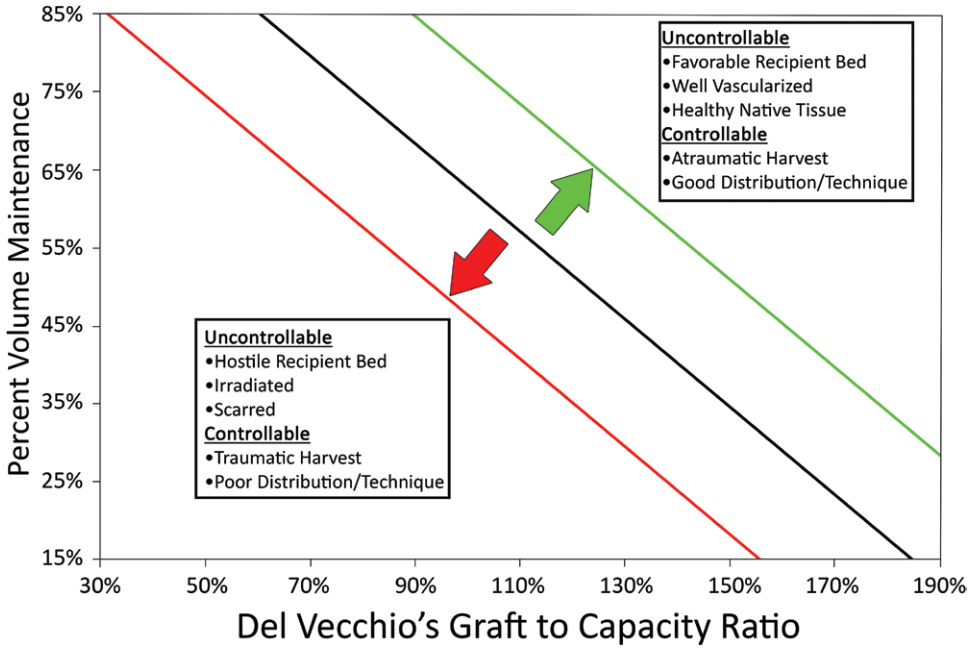

Fig. 8. Graft-to-capacity ratio and proposed shift in unfavorable recipient bed.

clinical observation appears to be congruent with a recent animal study in which negative-pressure external expansion of an irradiated tissue field failed to demonstrate an improvement in tissue perfusion.[22]

Despite an inability to "reshift the curve" and reverse the sequelae of radiation therapy, Brava does increase the absolute capacity by increasing the soft-tissue envelope. Thus, the benefit of using Brava for lumpectomy defects is manifested as an increased absolute fill volume while maintaining reasonable volume. This is reflected in our data, which demonstrated equivalent complications rates with Brava use but markedly higher fill volume (translating to improved results and/or fewer trips to the operating room).

Ultimately, the complication rate seems disconcertingly high when viewed as a common metric of success in plastic surgery. It is important to bear in mind that these complications in fat grafting (in comparison with complications for most other procedures) are generally minor and easily treatable, and do little to detract from an often otherwise acceptable result (Table 1).

Oncologic Safety

It seems intuitive to question the safety of any treatment that might be reformative in a previously treated tumor bed. The trepidation of safely fat grafting the breast, however, has slowly dissipated following continued investigation.[23] In addition to expert case series, sentinel articles by Rubin et al. and Gale et al. have further quelled concern regarding radiographic cancer surveillance and the notion of tumor up-regulation, respectively.[24–27] Although concerns have diminished in the setting of aesthetic augmentation, fat grafting to breast conservation therapy defects remains the most controversial application of fat grafting to the breast. It has been theorized that the regenerative effects of lipoaspirate may be counterproductive by stimulating nascent tumor cells, otherwise treated by radiation therapy and excision. Unlike fat grafting for aesthetic augmentation or total mastectomy, there are discordant data describing the oncologic safety profile.

The most seemingly disconcerting data were delivered by Petit et al. in a 2013 publication in the *Annals of Oncology* that describes a 5-year cumulative incidence of local events for noninvasive tumors to be considerably higher in the lipofilling cohort (18 percent) versus the nonlipofilling cohort (3 percent).[28] Quadrantectomy rather than mastectomy appeared to confer added risk. This startlingly high rate of local events may be explained by the fact that 42 percent of the patients had a close or positive margin in the lipofilling cohort (nearly two-fold higher than in the nonlipofilling cohort). This may be one of many reasons why this number is aberrantly high and conflicts with other published series. Even still, other series have demonstrated a subtly higher rate of locoregional recurrence with fat grafting breast conservation therapy defects. In

a well-designed case-control study by Gale et al., the breast conservation therapy lipofilling cohort had a locoregional cancer recurrence rate of 2.1 percent versus 1.1 percent for the nonlipofilling cohort. Although the increased rate of locoregional cancer recurrence with lipofilling was not statistically significant, the findings were unique to breast conservation therapy (rather than mastectomy) and should not be ignored. Thus, there is the continued need for further investigation.

There were no reports of locoregional cancer recurrence in our series, and modest rates of locoregional cancer recurrence appear to be similarly described in most other series. This is likely primarily a testament to consistently negative margins confirmed on final pathologic examination before undergoing fat grafting. In addition to negative margins, it has been speculated that an increased time from radiation therapy to lipofilling (specifically >24 months) may be protective against locoregional cancer recurrence. The mean time from radiation therapy to lipofilling in the series was rather lengthy (7 years). It is unclear whether this did in fact confer added safety, but it is the authors' belief that a modest delay from radiation to lipofilling should be considered to ensure oncologic safety.

Volume Augmentation and Study Limitations

Outcomes metrics have appropriately evolved from the borrowed nomenclature of skin grafting (i.e., percentage of "graft take") to the concept of "percentage augmentation." It is difficult, however, to define percentage augmentation for lumpectomy defects without a three-dimensional measurement of the actual defect (difficult to quantify even with advanced imaging). We do not provide a percentage augmentation for the patients in this study, but one must distinguish the prior publications that stress percentage augmentation. The concept of percentage augmentation originated from the need to demonstrate a large volume change to significantly enlarge an entire breast.

Conversely, a breast conservation therapy defect is a discrete defect of the breast that must be "filled," for lack of a better term. Without Brava, the mean volume of fat injected was approximately 50 cc. Assuming that there is some expected resorption (particularly with radiation therapy), that means only 20 to 30 cc of volume was corrected. Rare is the breast conservation therapy defect that is only 20 to 30 cc. Brava preexpands this tissue to allow for much greater volume to be injected. Again, assuming that there is some expected volume loss of the 250 cc, the remaining volume is much more likely to be adequate than the estimated 20 to 30 cc of true volume if one can only graft 50 cc. Thus, we do not feel that percentage augmentation values are critical in demonstrating the utility of Brava in this setting; nevertheless, the lack of quantitated preoperative and postoperative lumpectomy dimensions is an acknowledged limitation of the study.

There are additional limitations to the study that must be mentioned. The retrospective study design and small sample size limit the generalizability and strength with which conclusions from these data can be drawn. Furthermore, the mean follow-up time was 2.3 years. Ideally, all patients would have at least 5 years of follow-up. It bears mentioning, however, that the reported cases of locoregional cancer recurrence after lipofilling have generally been early (12 to 24 months).[28] Intuitively, if there is causation in terms of lipofilling and fat grafting, one would suspect the recurrence would be early rather than late (i.e., 4 to 5 years later). Therefore, the follow-up time in this study is somewhat suboptimal but reasonable based on precedent.

Prior experience with both internal and external tissue expansion in irradiated fields led to the modified Brava protocol by the senior author (L.P.B.). The protocol is 5 weeks of expansion compared with 3 weeks for patients undergoing aesthetic augmentation with Brava/fat grafting. The duration of Brava treatment is based on the collective anecdotal experience with Brava, and the necessity of extended treatment duration is neither confirmed nor invalidated by the data. Evidence-based Brava protocols—namely, indications for length of administration—have yet to be established.

CONCLUSIONS

Controversy regarding the clinical efficacy and oncologic safety of fat grafting breast conservation therapy defects is the end result of the duality with which surgeons view fat grafting. The transferred lipoaspirate is expected to reverse radiation damage (but not regenerate tumor) and yet, paradoxically, must also survive on the recipient bed as an avascular graft.

The clinical evidence provided in this article suggests that fat, as with any graft, performs suboptimally in a hostile recipient bed. Despite a higher complication rate than grafting healthy breast tissue, the authors believe that fat grafting for breast

conservation therapy defects retains a reasonable safety profile given the relatively minor complications observed and absence of cancer recurrence in this series. Brava preexpansion was associated with higher initial fill volume and may be used as an adjunctive means of improving efficiency in reconstructing breast conservation therapy defects.

Louis P. Bucky, M.D.
Division of Plastic Surgery
Pennsylvania Hospital Farm Journal Building
230 West Washington Square, Suite 101
Philadelphia, Pa. 19106
lbucky@drbucky.com

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