OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Breast

Maintaining Contour with a Three-dimensional Interstitial Tissue Marker in 134 Lumpectomies

Ashley T. Tsang, MD
Lawrence Cai, MD
Joanne Edquilang, MD
Irene L. Wapnir, MD

Background: Breast-conserving surgery (BCS) is meant to preserve the natural appearance of the breast; however, tissue volume deficits cannot always be compensated by soft tissue mobilization. A three-dimensional (3D) interstitial tissue marker (BioZorb) was designed to delineate the lumpectomy cavity for targeting boost irradiation, but an unexpected secondary benefit may be in guiding wound contraction and restoring contour to the lumpectomy bed. We analyze tissue volume excised at the time of lumpectomy as a function of device size selected.

Methods: In total, 134 consecutive lumpectomy patients implanted with BioZorb between May 2015 and February 2020 were retrospectively analyzed for tissue volume excised, device size used, location, and re-operation rates, including explantation of the device.

Results: An estimated 113 patients underwent device implantation at initial lumpectomy, and 21 at margin re-excision. Twenty-seven patients underwent re-excision, while 14 elected mastectomy for positive margins following insertion; 22 had the same device reimplanted. Mean lumpectomy volume was 79.0 cm^3 (range 10.3–275.8 cm^3) during the first implant procedure. Large-volume lumpectomies, averaging 136.5 cm^3, were associated with selection of larger devices, which aided in restoring volume and maintaining breast contour. Three (2.2%) patients requested removal of the device.

Conclusions: BioZorb implantation can be a safe and useful oncoplastic technique for restoring volume with BCS. Large-volume lumpectomies can be performed without contouring defects using the device. An unexpected secondary benefit of the device may be scaffolding for wound contraction. *(Plast Reconstr Surg Glob Open 2021;9:e3696; doi: 10.1097/GOX.0000000000003696; Published online 30 July 2021.)*

INTRODUCTION

An estimated 281,550 new cases of breast cancer will be diagnosed among women in the United States in 2021.[1] Advances in the treatment of breast cancer continue to improve survival rates, and as such, there is an increasing emphasis on survivors' quality of life. Preserving and restoring the natural appearance of the breast after breast-cancer–related surgery is widely recognized as desirable.[2] Soft tissue mobilization and oncoplastic techniques have been championed to offset defects or asymmetry created during breast-conserving surgery (BCS).[3,4] As expected, large excisions can result in contouring defects. However, even small lumpectomies, depending on their location or the size of the breast, can also cause significant deformities. The extent of resections is aggravated by the impetus to achieve tumor-free lumpectomy margins, leading to routine practices of shaving additional margin tissue.[5]

The vast majority of patients treated by BCS receive adjuvant breast irradiation. Radiation oncologists and physicists rely on the presence of metallic clips, soft tissue changes in the surgical bed, or seromas to design treatment plans that can accurately target the tumor bed.[6–8] Boosting of the lumpectomy cavity is associated with lower local recurrence rates.[9–11] Partial breast irradiation has also emerged as a modality comparable to whole breast irradiation in select patient populations.[12] For these patients, constraining the radiation fields to the lumpectomy cavity and a surrounding margin are even more critical.

BioZorb—the 3D bioabsorbable interstitial tissue marker containing six titanium clips (Hologic Inc,

From the Department of Surgery, Stanford University School of Medicine, Standford, Calif.

Received for publication December 6, 2020; accepted May 13, 2021.

Drs. Tsang and Cai contributed equally to this work.

DOI: 10.1097/GOX.0000000000003696

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

formerly Focal Therapeutics; Sunnyvale, Calif.)—was introduced to provide better conformal delineation of the lumpectomy cavity for radiotherapy targeting and has been described to offset the volume loss and improve contouring.[13–15] In a recent multicenter study of 818 lumpectomy-treated women, the 6-, 12-, and 24-month reported outcomes with this device were graded as good to excellent by 92.4% and 87.3%, respectively, by patients and surgeons alike.[16] We hypothesized that good contouring is guided by device size selection in relation to the tissue volume excised during lumpectomy, serving as a scaffold during the period of wound contraction and healing. This retrospective study reports our experience on the first 135 BioZorb devices implanted in conjunction with BCS in 134 consecutive patients.

MATERIALS AND METHODS

Institutional review board approval was obtained for this retrospective chart review of 134 consecutive patients who underwent implantation of a BioZorb interstitial tissue marker by a single surgeon. In general, a device was inserted when the volume of the defect was large with respect to the size of the breast or location and when there was insufficient tissue to mobilize to correct the defect. The spiral shaped BioZorb comes in six sizes (2 × 2, 2 × 3, 3 × 3, 3 × 4, 4 × 4, and 4 × 5 cm) with six titanium clips in each.[16] Only three flat profile devices are available, ranging from 2 × 1 to 3 × 1 cm. Lumpectomy cavity dimensions were assessed using spiral-shaped metallic sizers. Briefly, the BioZorb was anchored with 3-0 polydioxanone sutures into the breast tissue surrounding the lumpectomy cavity in at least three axis points. Soft tissue mobilization was routinely used to drape over the device. Tumor laterality, quadrant location, tissue volume excised, and size selection of the device were recorded. Need for re-operation and management of the device during re-excision lumpectomies are described. Primary outcomes include postoperative complications. Secondary outcomes include additional surgery for device explantation at patient request.

Lumpectomy tissue volumes were analyzed in this consecutive cohort as a function of device size selected. The prolate ellipsoid formula was used to calculate excised tissue volume [$(4/3\pi)\ a \times b \times c$, where *a, b,* and *c* refer to the radius or half the diameters of the lumpectomy specimen specified in the pathology report]. The same formula was used to calculate volume replaced based on BioZorb dimensions. However, shaved margin volume was calculated using the rectangular formula $a \times b \times c$, where *a, b,* and *c* represent the height, width, and depth of tissue excised and reported by pathology. The amount of tissue excised at lumpectomy was correlated to the volume of the interstitial marker inserted. In cases where the initial device was inserted at re-excision, tissue volume excised was calculated using the volume removed at initial lumpectomy plus the volume of the margins taken at re-excision. Excluded from the volume calculations were patients who had bilateral breast reductions concurrent with the lumpectomy surgery, insertion of a flat-profile device, initial excisions at an outside facility, or two devices inserted for multicentric disease. Impressions regarding contouring of breast were reviewed in progress notes. Photography was not consistently documented in the medical chart.

RESULTS

Between May 2015 and February 2020, 133 women and one man underwent implantation of BioZorb device(s) during BCS. The median age was 57 years (29–78) and median BMI 26 kg/m^2 (18–70). One woman had two devices implanted simultaneously for upper and lower quadrant resections, bringing the total of devices used for index cancer resections to 135. The most common indications for lumpectomy were invasive ductal carcinoma (70.1%), ductal carcinoma in situ (DCIS, 17.2%), and invasive lobular carcinoma (9%) (Table 1). The median follow-up was 28 months (range 4–60 months).

In total, 113 devices were placed at initial lumpectomy, while 21 were initially placed at the time of re-excision lumpectomy. Twenty-seven patients required re-excision lumpectomy for positive margins, with one patient requesting device removal at the time of re-excision lumpectomy; 22 had the same device re-inserted, and four underwent exchange for a different size. Three patients underwent marking of the tumor bed with the device for lumpectomies performed with a simultaneous mastopexy or reduction mammoplasty. One patient experienced a postoperative hematoma that led to re-operation for evacuation and washout, leaving the device in place. There were no infections despite reinsertion of the same device during subsequent re-excision surgery for positive margins.

Fourteen devices were explanted at the time of completion mastectomy for persistently positive margins. One patient opted to have bilateral mastectomies based on her inherited disposition for breast cancer. Another woman had it inadvertently explanted during a subsequent bilateral breast reduction operation. A total of three (2.2%) patients requested to have the marker removed due to anxiety over palpation of the device, one during re-excision for positive margins, and two as an additional procedure (Table 2).

Typical observations in the clinical medical record describe the device as not palpable, associated with vague fullness or simply palpable. Patient impressions were not systematically recorded. After about 2 years, most devices were no longer detected on physical examination.

The devices implanted in our series ranged in size from 2 × 2 cm to 4 × 5 cm with corresponding volumes of 4.2 cm^3

Table 1. Histopathology

	Patients, n (%)
Invasive ductal carcinoma	94 (70.1)
Ductal carcinoma in situ	23 (17.2)
Invasive lobular carcinoma	12 (9.0)
Pleomorphic LCIS	1 (0.75)
Adenoid cystic carcinoma	1 (0.75)
Malignant phyllodes	1 (0.75)
Sarcoma	1 (0.75)
ADH with history of breast cancer	1 (0.75)

Table 2. Initial Implantation and Re-operations

	Patients, n (%)
Initial placement	134
Lumpectomy alone	110 (82.1)
With mammoplasty	3 (2.2)
Re-excision lumpectomy	21 (15.3)
Second surgery for positive margins	41 (30.6)
Re-excision lumpectomy with	27 (20.1)
reimplantation of same size device	22 (81.5)
Implantation of different size device	4 (14.8)
Removal of device*†	1 (3.7)
Mastectomy	14 (10.4)
Additional surgery with removal of device	4 (3.0)
Explantation alone*†	2 (1.5)
Reduction mammoplasty	1 (0.75)
Bilateral mastectomy for genetic predisposition	1 (0.75)

*One patient requested removal of the device and subsequently underwent mastectomy.
†A total of 3 patients requested removal of the device.

to 41.9 cm^3 (Fig. 1). Low profile or flat devices, sizes of 1 × 2 cm to 1 × 3 cm, were selected for four patients. The most common lumpectomy location with BioZorb placement was the upper outer quadrant of the breast (37%) followed by the lower outer quadrant (35.6%) (Fig. 2A). A radar plot is used to show the distribution of cases by device size and location (Fig. 2B). The 2 × 2 cm size was most often selected for the upper inner quadrant, while 2 × 3 cm devices were prevalent in the lower outer quadrant. Larger implants, 3 × 3 and 3 × 4 cm, were most often selected for upper outer quadrant cancers. Interestingly, the largest implant size, 4 × 5 cm, was equally distributed in all four quadrants, suggesting use in a more central aspect of the quadrant to conserve nipple–areolar complex projection.

The average volume of tissue excised during lumpectomy for the entire cohort was 79.0 cm^3 (range 10.3–275.8 cm^3). The mean volume of tissue excised corresponding to the size and volume of devices is shown for 123 lumpectomies, excluding 11 cases (four low profile, three concurrent bilateral breast reductions, two re-excision cases from outside facilities, and one patient with multicentric disease requiring two devices). Tissue volumes ranged from 32.8 to 82.5 cm^3 for lumpectomy only, and 52.1 to 136.5 cm^3 with added volume of shave margins (Fig. 1). As expected, the size of implant selected increased with average tissue volume excised. Shave margins nearly doubled the volume of tissue removed. For example, large volume lumpectomies which we define as requiring the largest device (4 × 5) averaged 136.5 cm^3; comparable to 3.5 golf balls. Despite under-replacement of tissue volume, satisfactory contouring was achieved as depicted in Figure 3. In Figure 3A, the patient underwent a 167.2 cm^3 lumpectomy of the upper inner quadrant and was implanted with a 4 × 5 cm device.

Postoperatively, a large seroma filling the lumpectomy cavity was aspirated, resulting in contour deformity. However, by 5 weeks, wound healing and contraction occurred resulting in correction of the contour defect without recurrence of a seroma. Excellent contour was sustained following whole breast irradiation and on one year follow-up. Similarly, satisfactory contouring was achieved after upper outer quadrant and lower inner quadrant lumpectomies, 8 months and 1 year post surgery (Fig. 3B,C). Incorporation of the device into surrounding breast tissue was evident in mastectomy specimens (Supplemental Figure 1A). Experience with metachronous implantation of a second device is shown in Supplemental Figure 1B and 1C following repeat lumpectomy for an invasive in-breast recurrence, 18 months later. (**See Figure, Supplemental Digital Content 1**,

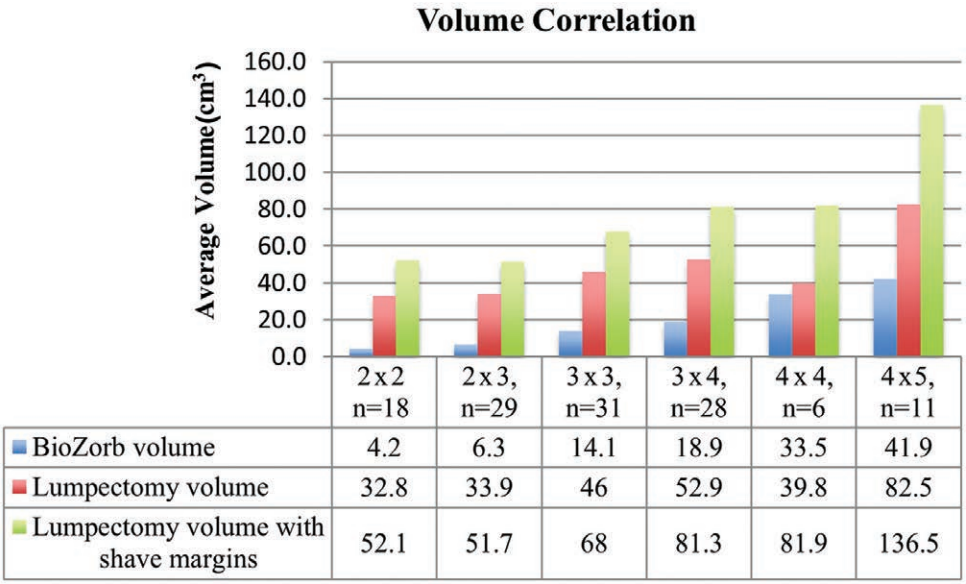

Fig. 1. Volume analysis in 123 lumpectomies. Comparison of device volumes according to size of BioZorb (blue) to average volume of tissue excised in lumpectomies (orange) and lumpectomy plus extra shave margins (gray) tissue volumes. Additional shave margins nearly doubled the amount of tissue excised during lumpectomy.

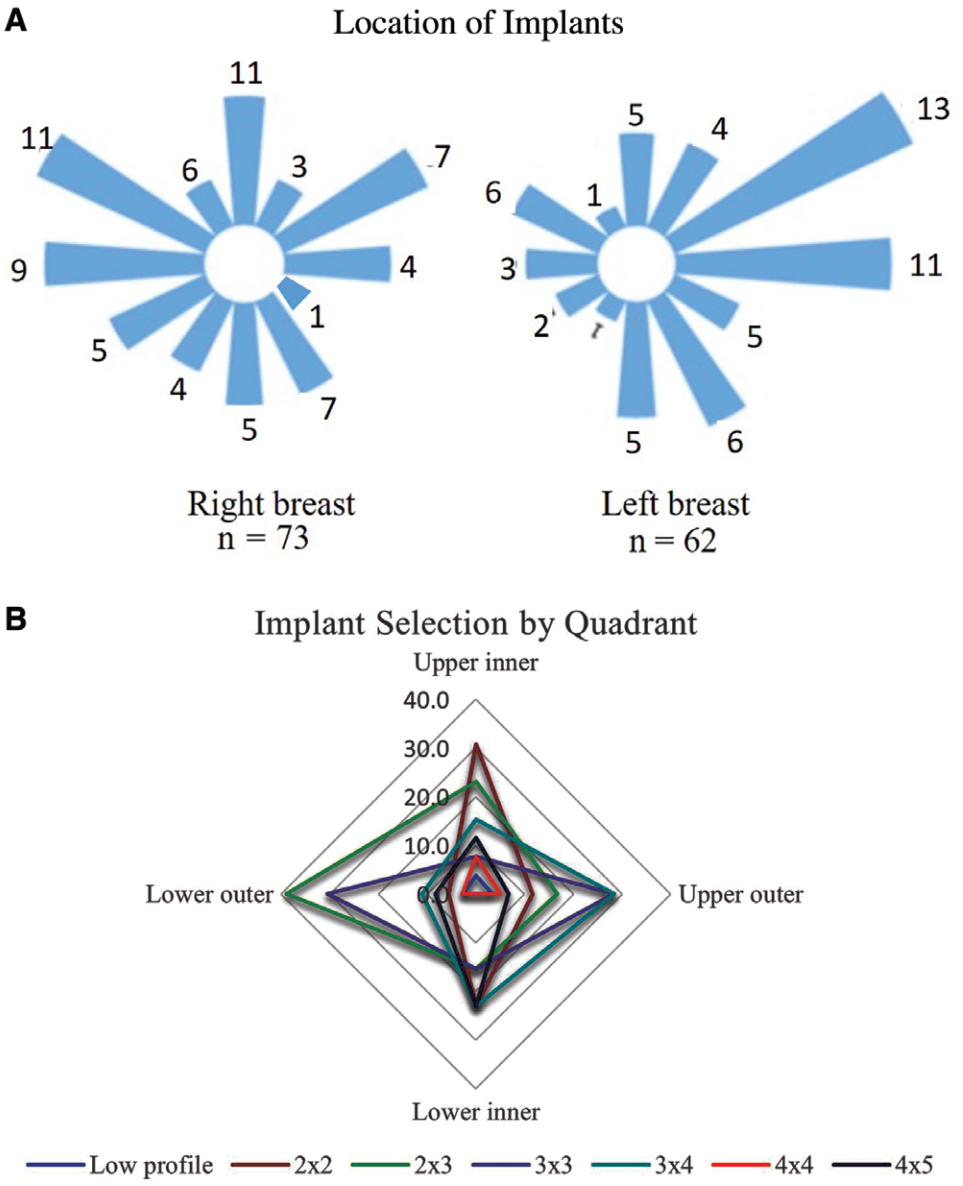

Fig. 2. Location of implants. A, Each bar corresponds to the radial position on the breast. The majority of devices were implanted in the upper outer (37%) and lower outer (35.6%) quadrants of the breasts. B, Implant selection by quadrant. The radar plot depicts device sizes used per breast quadrant; 2 × 2 cm were prevalent in the upper inner quadrant, 2 × 3 cm in the lower outer quadrant, 3 × 3 and 3 × 4 cm in the upper outer quadrant, and 4 × 5 cm, evenly distributed in all four quadrants.

ex vivo and mammographic appearance of device. A, The device is well incorporated without seroma in a mastectomy specimen. B, Spot magnification view of fine, pleomorphic calcifications identified on annual mammogram, which proved to be an in-breast tumor recurrence. **http://links.lww.com/PRSGO/B710**.)

DISCUSSION

This is one of the largest single-institution series examining utility of BioZorb interstitial tissue markers for breast-conserving surgery. We focused on correlating volume deficits created during initial lumpectomy and subsequent re-excision operations to device size. One of the benefits of the 3D interstitial marker is that it defines the tumor bed more accurately for radiation oncologists, allowing them to ignore nontumor-related soft tissue changes caused by wire localization procedures or oncoplastic soft tissue mobilization performed to correct contouring defects. For breast surgeons, the presence of the device is especially useful in cases requiring re-excision lumpectomy for the same reasons described above. Recently, Srour and Chung published their short- and long-term outcomes of using the implantable device in 89 patients, reporting a 5.5% rate of infectious complications and a case of device migration.[17] Kaufman et al reported on the BioZorb registry findings encompassing 14 sites,

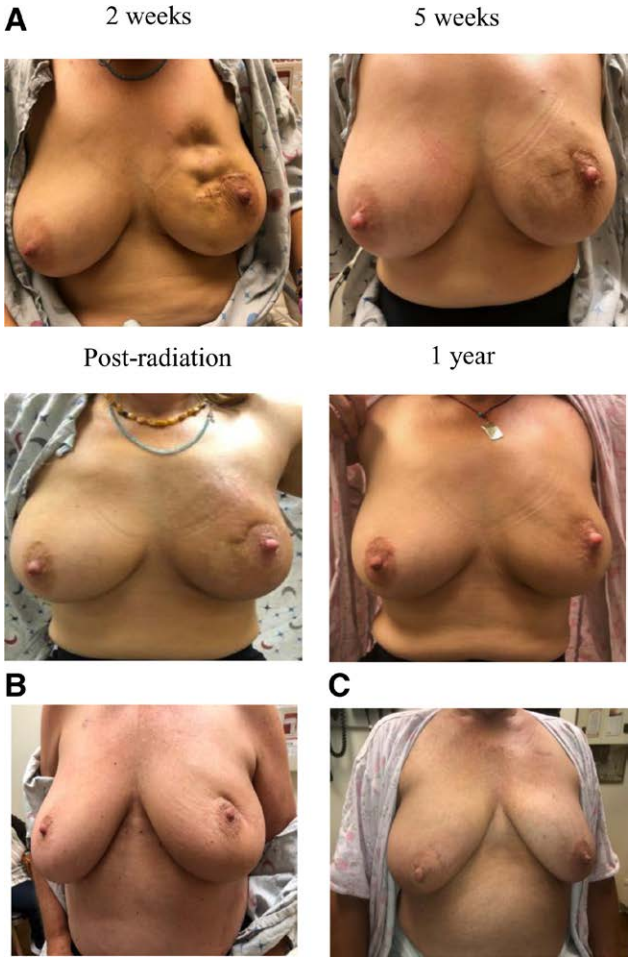

Fig. 3. Large volume lumpectomy. A, Serial photographs of a patient who had 167.2 cm^3 of breast tissue excised from the upper inner quadrant for a 6.3 cm ductal carcinoma in situ, roughly equivalent to the volume of four golf balls. Soft tissue mobilization and implantation of a 4x5 cm spiral interstitial tissue marker was implanted. At 2 weeks, contour deformity following seroma aspiration; 5 weeks postoperative showing improved breast contouring without recurrent seroma; 1 month post whole breast irradiation and 1 year post-lumpectomy. B, Another patient with excellent breast contour 8 months after large volume lumpectomy in the upper outer quadrant with insertion of a 4 x 5 cm device and postoperative whole breast irradiation. C, Another example of contour preservation 1 year following large volume lumpectomy in the lower inner quadrant and insertion of a 4 x 5 cm device with completion of whole breast irradiation.

42 surgeons and 818 patients.[16] In their study, 73.1% of devices used were 2 × 2 or 2 × 3 cm, whereas only 38.2% of our cases were in this device size range. Helping to improve cosmesis and scaffolding for oncoplastic closure was noted as an attribute of the device in 62% and 49% of cases. The rate of device removal was 2.7%, comparable to the 2.2% in our series. We report a higher conversion to mastectomy, 10.4%, not surprising given the proportion of large volume lumpectomies and use of larger devices. There were no infectious complications in our study cohort, even with reinsertion of the same device in 22 of 27 re-excisions, notably a cost-effective measure.

Radiation oncologists appreciate the placement of a 3D interstitial marker, as it demarcates the lumpectomy cavity with greater precision and more accurate contouring of the tumor bed. Moreover, it allows radiation physicists to constrain the radiation field plans either for the lumpectomy cavity boost or in the case of partial breast irradiation.[18–20] The semi-rigid scaffold of the interstitial tissue marker also serves to maintain the form of the breast during wound healing, leading to good cosmetic outcomes. In this regard, it is envisioned that the device guides tissue remodeling to some extent and prevents wound contraction into the defect. Implanting the device is relatively straightforward, adds minimal time to the operation and reduces the need for tissue mobilization and rearrangement required to obliterate the lumpectomy cavity defect. In our experience, the placement of the device is also an asset for cases requiring margin re-excision, as it facilitates the identification of the lumpectomy cavity.

Using the 3D interstitial tissue marker, BioZorb, as an adjunct for breast reconstruction at the time of lumpectomy operations or subsequent re-excisions is a safe and effective method that can partially restore volume and asymmetry. The device resorbs very slowly, over 24 months or more. Based on the patients who underwent mastectomy, all within 6 months of their index procedure, the device appeared grossly well incorporated into the surrounding breast tissue and without evidence of seromas. (**Supplemental Figure 1, http://links.lww.com/PRSGO/B710**). In the end, there is no true long-term replacement of volume as the wound progressively contracts. However, the presence of the device acts as a scaffold to promote 360 degree or three-dimensional wound contraction as healing occurs and throughout the process of scar remodeling. It seems that this uniquely prevents flattening and retraction of skin and subcutaneous tissues down to chest wall in cases. Moreover, it is important to point out that the presence of the BioZorb did not interfere with or delay the diagnosis of in-breast recurrences, both of which were easily detected on breast imaging studies.

We found that patients were overall satisfied with the device, even when clinically palpable, because only three requested explantation. The palpability of the device has been a criticism. This is less of an issue for deeper lumpectomy cavities whereby part of the device circumference is covered by surrounding breast tissue. It is important though, to make patients and other health professionals examining these women aware of the potential for a mass-like effect at the surgical site to not raise suspicions of local recurrence. Most patients in this cohort did not mind feeling the rounded fullness associated with the 3D interstitial marker.

Maintaining the shape and contour of a breast following lumpectomy, particularly after resection of large lesions or subsequent re-excisions is a real concern. Advances in treatment of breast cancer have increased survivors' quality of life.[21] Many randomized, prospective clinical trials examining locoregional breast cancer treatments involving patient-reported outcomes include cosmetic results. Poor aesthetic outcome due to contour defects, shrunken breast volume after breast

irradiation, and asymmetry with contralateral breast following BCS are still associated with stigmatization, depression, and worse quality of life measures.[22,23] One of the shortcomings of our retrospective analysis is that we did not evaluate cosmetic outcomes with any instrument nor survey patients regarding their satisfaction with this technique. In reality, these impressions are qualitative because one can only speculate on how the same breast would have appeared without the use of the BioZorb. Of note, there was a slight decline in the benefit of the device as reported by surgeons participating in the registry over time, from 78% to 67% for 6 and 24 months, respectively.[16]

CONCLUSIONS

Although the 3D interstitial tissue marker engineered to delineate the tumor bed for radiation planning does not completely restore the volume of the breast when implanted during breast conservation surgery, it should be considered an oncoplastic strategy because it is safe and provides a scaffold for wound healing that can minimize contouring deficits, especially in large volume lumpectomies. Long term follow-up studies are warranted to document late aesthetic outcomes.

Irene L. Wapnir, MD
Professor of Surgery
Department of Surgery
Stanford University School of Medicine
300 Pasteur Drive #H3591
Stanford, CA 94305
E-mail: wapnir@stanford.edu

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. *CA Cancer J Clin.* 2021;71:7–33.
2. ASPS Public Relations. *ASPS National Clearinghouse of Plastic Surgery Procedural Statistics.* Arlington Heights, Ill.: ASPS; 2016.
3. De La Cruz L, Blankenship SA, Chatterjee A, et al. Outcomes after oncoplastic breast-conserving surgery in breast cancer patients: a systematic literature review. *Ann Surg Oncol.* 2016;23:3247–3258.
4. Veiga DF, Veiga-Filho J, Ribeiro LM, et al. Evaluations of aesthetic outcomes of oncoplastic surgery by surgeons of different gender and specialty: a prospective controlled study. *Breast.* 2011;20:407–412.
5. Chagpar AB, Killelea BK, Tsangaris TN, et al. A randomized, controlled trial of cavity shave margins in breast cancer. *N Engl J Med.* 2015;373:503–510.
6. Machtay M, Lanciano R, Hoffman J, et al. Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys.* 1994;30:43–48.
7. Sharma R, Spierer M, Mutyala S, et al. Change in seroma volume during whole-breast radiation therapy. *Int J Radiat Oncol Biol Phys.* 2009;75:89–93.
8. Oh KS, Kong FM, Griffith KA, et al. Planning the breast tumor bed boost: changes in the excision cavity volume and surgical scar location after breast-conserving surgery and whole-breast irradiation. *Int J Radiat Oncol Biol Phys.* 2006;66:680–686.
9. Bartelink H, Horiot JC, Poortmans P, et al; European Organization for Research and Treatment of Cancer Radiotherapy and Breast Cancer Groups. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med.* 2001;345:1378–1387.
10. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys.* 2011;81:59–68.
11. Vrieling C, van Werkhoven E, Maingon P, et al; European Organisation for Research and Treatment of Cancer, Radiation Oncology and Breast Cancer Groups. Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC boost vs no boost trial: a randomized clinical trial. *JAMA Oncol.* 2017;3:42–48.
12. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol.* 2017;7:73–79.
13. Kaufman CS, Hall WH, Wolgamot GM, et al. Clinical use of a three-dimensional tissue marker to target postlumpectomy radiation. *J Clin Oncol.* 2015;33:53.
14. Cross MJ, Lebovic GS, Ross J, et al. Impact of a novel bioabsorbable implant on radiation treatment planning for breast cancer. *World J Surg.* 2017;41:464–471.
15. Harman J, Govender S, Simpson J, et al. A new method for partial breast reconstruction: 3-year New Zealand experience. *Plast Reconstr Surg.* 2019;143:49–52.
16. Kaufman CS, Cross MJ, Barone JL, et al. A three-dimensional bioabsorbable tissue marker for volume replacement and radiation planning: a multicenter study of surgical and patient-reported outcomes for 818 patients with breast cancer. *Ann Surg Oncol.* 2021;28:2529–2542.
17. Srour MK, Chung A. Utilization of BioZorb implantable device in breast-conserving surgery. *Breast J.* 2020;26:960–965.
18. Wiens N, Torp L, Wolff B, et al. Effect of BioZorb surgical marker placement on post-operative radiation boost target volume. *J Radiat Oncol.* 2018;7:175–179.
19. Foster B, Sindhu K, Hepel J, et al. Three-dimensional bioabsorbable tissue marker placement is associated with decreased tumor bed volume among patients receiving radiation therapy for breast cancer. *Pract Radiat Oncol.* 2019;9:e134–e141.
20. Brouwers PJAM, van Werkhoven E, Bartelink H, et al; Young Boost Trial research group. Predictors for poor cosmetic outcome in patients with early stage breast cancer treated with breast conserving therapy: results of the Young boost trial. *Radiother Oncol.* 2018;128:434–441.
21. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin.* 2019;69:363–385.
22. Moyer A. Psychosocial outcomes of breast-conserving surgery versus mastectomy: a meta-analytic review. *Health Psychol.* 1997;16:284–298.
23. Waljee JF, Hu ES, Ubel PA, et al. Effect of esthetic outcome after breast-conserving surgery on psychosocial functioning and quality of life. *J Clin Oncol.* 2008;26:3331–3337.