Advances in Radiation Oncology (2021) 000, 100848

advances in radiation oncology

www.advancesradonc.org

Critical Review

Review of Current Accepted Practices in Identification of the Breast Lumpectomy Tumor Bed

Pascal Acree,[a,b,*] Amee Kapadia,[b] Ronak Mahatme,[b,c] Lucia Zhang,[b,d] Darsh Patel,[b] Charlie Almoney,[b] Geonwoo Park,[b] Morgan Kofsky,[b] Shababa Matin,[b] and Mehran Habibi, MD[e]

[a]Medical College of Georgia, Augusta University/University of Georgia Medical Partnership, Athens, Georgia; [b]Department of Biomedical Engineering, Johns Hopkins University, Baltimore, Maryland; [c]University of Connecticut School of Medicine, Farmington, Connecticut; [d]UT Southwestern Medical School, Dallas, Texas; [e]Department of Surgery, Johns Hopkins Hospital, Baltimore, Maryland

Received July 13, 2021; revised October 8, 2021; accepted November 1, 2021

Abstract

Purpose: Of the 260,000 women diagnosed with breast cancer annually in the United States, more than 60% are treated with breast-conserving surgery or lumpectomy, followed by radiation to decrease the chance of local recurrence. More than 70% of breast cancer recurrences are localized to the original tumor cavity. Hence, targeted radiation therapy after lumpectomy is critical for recurrence prevention. With 30,000 patients annually opting for oncoplastic reconstruction of the breast after lumpectomy to improve cosmesis, the resulting tissue rearrangement increases the difficulty for radiation oncologists to accurately delineate the cavity when planning radiation therapy. Owing to the absence of a standardized protocol, it is important to assess the efficacy of various methods used to mark the tumor cavity for improved delineation.

Methods and Materials: A keyword search and analysis was used to compile relevant articles on PubMed (National Center for Biotechnology Information).

Results: Currently, a common practice for tumor cavity localization is applying titanium surgical clips to the borders of lumpectomy cavity. Tissue movement and seroma formation both impact the positioning of surgical clips within the tumor cavity and lead to significant interobserver variability. Furthermore, the main application of surgical clips is to control the small vessels during surgery, and that can create confusion when the same clips are used for tumor bed localization. All alternative solutions present more precise tumor bed delineation but possess individual concerns with workflow integration, patient comfort, and accuracy. Though liquid-based fiducials were found to be the most effective for delineating tumor cavities, there are still drawbacks for clinical use.

Conclusions: These findings should encourage medical innovators to develop novel techniques for tumor cavity marking to increase delineation accuracy and effectively target at-risk tissue. Future solutions in this space should consider the properties of liquid-based fiducial markers to improve radiation oncologists' ability to precisely delineate the tumor cavity.

Sources of support: All authors received no financial support for the research, authorship, and/or publication of this article.

Disclosures: All authors declare inventor status on a provisional patent application (U.S. 63/027,959, Cavity-Adhering Fiducial Gel for Comprehensive Radioplanning Visualization) through the USPTO.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Pascal Acree; E-mail: pacree@augusta.edu

https://doi.org/10.1016/j.adro.2021.100848

Introduction

Of the 260,000 women diagnosed with breast cancer annually in the United States, more than 60% are treated with breast-conserving surgery (BCS) or lumpectomy followed by targeted radiation therapy (RT). Immediately after tumor resection, the pathologist evaluates the surgical margins of the specimen to determine whether they are free of cancer cells. This guides the surgical oncologist as to whether a re-excision is needed. Once the margins are negative, the patient would start the next step of care, including subsequent radiation therapy and/or systemic therapy.[1]

Currently, 30,000 BCS patients per year undergo oncoplastic reconstruction of the breast after lumpectomy to improve cosmetic outcomes. This involves reduction mammoplasty or lift procedure on the same side and symmetry operation of the contralateral side.[1] These procedures are increasingly performed immediately after and in conjunction with the lumpectomy and serve to remove unnecessary skin, flatten the tumor bed (TB) and improve overall breast cosmesis. In the weeks after the procedure, radiation oncologists approximate the location and volume of the tumor cavity using the available visual markers to plan targeted radiation therapy. Radiation oncologists use computed tomography (CT) to simulate the lumpectomy cavity and design the radiation plan to minimize any unnecessary radiation to vital organs such as the lung and heart. Given that the margins and tissue around the tumor bed can be rearranged during oncoplastic reconstruction, it becomes increasingly difficult for radiation oncologists to precisely delineate the cavity. Imprecise delineation of the postlumpectomy tumor bed increases the chances of ineffective radiation therapy with less accurate targeting of the true tumor cavity. Inaccuracy in the location of the radiation boost can lead to radiation side effects in the case of excess dosage or increased risk of cancer recurrence in the case of inadequate targeting of the cavity.[2]

Surgical oncologists send the entire specimen from the tumor resection to pathology for evaluation, where the specimen gets sliced, processed, dyed, and assessed under the microscope for positive margins. A positive margin occurs when the cancer is found to reach the edge of the excised tissue, indicating that cancerous cells might have remained in the patient. Around 10% to 20% of patients undergoing breast-conserving surgery have at least 1 margin come back positive and require a re-excision operation.[3] When all margins are clear of cancer, the patient proceeds to breast radiation therapy. Based on the optimal course of treatment, 75% to 85% of patients undergo whole-breast irradiation (WBI) with the addition of a high-dose radiation boost targeted to the cavity in selected groups of patients. The remaining 15% to 25% receive partial breast irradiation (PBI) treatment, where radiation is focused solely on the cavity and a small portion of breast around the cavity in higher doses over a shorter period of time. Ultimately, 70% of cancer recurrences are localized to the original tumor cavity, rendering follow-up irradiation of the area a critical step in treatment efficacy and recurrence prevention.[4] Accurate localization of tumor, detailed orientation of the specimen, clear marking of the lumpectomy cavity, and delineation of the tumor bed are important factors in successful breast-conserving surgery and in the case of positive margins for planning the re-excision surgery. Only after that will radiation therapy start.[5] This review will provide an overview of current methods used to mark the tumor cavity for improved delineation as well as address their shortcomings in current clinical applications.

Methods

To provide an in-depth overview of current methods used to mark the tumor cavity for improved delineation as well as address the respective shortcomings in each of these methods, a keyword search and analysis approach was used to compile relevant articles on PubMed (National Center for Biotechnology Information). Some of the keywords and phrases used to search for articles pertaining to tumor cavity delineation included breast-conserving surgery, lumpectomy, markers, breast cavity markers, tissue markers, surgical clips, and breast tumor bed. Five reviewers examined the compiled index of papers and then filtered based on whether the technology or method presented had been clinically assessed. Relevant researcher testimony, experimental data, and statistics from the filtered research articles were included in the comprehensive literature review.

Additional selection criteria used to determine the relevancy of papers included a date of publication from the year 2000 or later, publication originally in the English language, and peer-review verification in academic journals. These metrics were chosen to guarantee the information was in accordance with modern medical standards and procedures, avoid misinterpretations of data that could arise in translation, further validate the findings with the credibility of the sources, and maintain a common general subject area across articles. To assess all clinically used technologies and methods in this space, patient size of the study was not set as an exclusion criterion.

After the determination of each respective paper as relevant to the overarching focus, the remaining researchers on the team reviewed its inclusion in a particular section of the literature review. The accumulation of the above systematic processes resulted in the construction and authoring of this review. The review is fully supported by cited literature and provides an overview of the current state of postoperative tumor bed identification through the use of tumor bed delineation techniques.

Discussion

Current gold standard of care

Identification of cavity

Presently, there is no standardized protocol for marking the margins of the lumpectomy cavity.[4] Current methods to identify the cavity rely on clinical notes, seroma formation, position of lumpectomy scar, or ligation clip placement, all of which were discovered to have associated drawbacks. The 3 main methods for delineation—clinician discretion, seroma formation, and ligation clips—are described herein.

Surgeon discretion with no marker

Some radiation oncologists rely on the lumpectomy incision site as an indicator of the tumor bed. This method renders localization and differentiation of individual margins within the tumor bed nearly impossible, and also leads to inaccuracies in identifying the tumor bed in the first place. Krawczyk and Engel found that basing radiation dosing on surgical scar location results in inadequate radiation coverage, regardless of whether the scar is located relative to the tumor borders.[6] In fact, they found that the closer the scar is to the breast tissue border, the higher the risk of inadequate coverage with standardized beams. Hence, reliance on the lumpectomy scar alone to locate the tumor bed will result in significant risk of underdosing the lumpectomy cavity and is not sufficient for radiation planning decisions. In a study conducted at Fox Chase Cancer Center, 4 hypothetical fields based on lumpectomy scar were compared with the actual location of the tumor bed based on surgical clips. The center of the hypothetical field was the center of the scar. When margins were equal to half the scar length, inadequate coverage was found 51% of the time.[7] As a result, it was concluded that the lumpectomy scar is a poor indicator of the tumor bed location.[6,7]

Seroma formation

Seroma (postoperative serous fluid accumulation) fills the cavity after lumpectomy and may be visualized on CT using the color difference between fluid and soft tissue. However, the formation of seroma is variable and not always localized to the tumor cavity as it can diffuse to other areas of the breast.[8,9] The amount of seroma present depends on the individual patient's breast parenchyma density and time elapsed after surgery, as the amount reabsorbed into the cavity increases with time. Seroma formation also relies on how the excision cavity is closed. For example, less seroma volume forms in cases with full-thickness cavity closure.[8] As a result, reliance on seroma formation alone often leads to imprecise localization of the tumor bed. According to Coles et al, where seroma formation on 30 patients was judged by 2 clinical oncology consultants, 8/30 patients had "highly visible" seroma formation, 10/30 had "visible" seroma formation, 6/30 had "subtle" seroma formation, and 6/30 had seroma formation that was "not visible" on CT after surgical closure of the breast after BCS.[4] In another study, researchers found that seroma formation could be observed on CT for 65% of patients, with a median of 35 days between BCS and CT.[10] Seroma formation is variable and unreliable when delineating the tumor cavity to plan clinical target volume (CTV) for radiation therapy, which includes the gross tumor volume plus an additional margin. Without any kind of fiducial markers, the tumor bed can be underdosed and healthy tissue can be unnecessarily dosed as a result of an inaccurately determined CTV.

Titanium clips

Many surgeons place small radiopaque titanium clips into the cavity before closing the patient, which are visualized on CT scans. The use of clips and analogous fiducial markers is hailed as the "current gold standard" because it provides additional information about the sides of the cavity that seroma formation may not provide.[11] In fact, several studies have supported the use of clips in preventing underdosing of the cavity compared with dosing based on seroma formation.[9] The number and placement of the clips depends on the surgeon.[4] Kirby et al found 5 clips to be the optimal number to mark the 6 sides of the cavity, with 4 placed radially and 1 placed deep into the tissue.[11] When 5 clips were used, the additional margin required to be added to the CTV was reduced from 8 mm (added when no clips were used) to 2 mm, minimizing the potential radiation of healthy tissue. However, clinicians have not standardized their usage of ligation clips, which causes variability even within specific medical centers. For instance, 1 study noted that within 1 institution, only 44% of tumor beds had at least 1 clip.[12] Out of these clipped tumor beds, 66% contained 1 to 5 clips, 22% contained 6 to 10 clips, and 12% contained more than 10 clips.

Use of clips in tumor cavity delineation is especially helpful when a significant amount of time has elapsed between lumpectomy and radiation therapy as seroma is less visible and the cavity changes over time. A common case for this is when a patient undergoes chemotherapy after surgery.[8] Clips also give a more consistent definition of the cavity, reducing interobserver variability and improving overall radiation planning reliability.[9] When clips are used for marking, the conformity index is only 65%, representing a high level of interobserver variability. Furthermore, clips are only point markers, meaning the radiation oncologists still have to interpolate the boundaries of the cavity between the clips. They also provide no information about the location of the tumor in relation to the boundaries of the cavity, leaving the issue of margin discrimination unaddressed.[9] A 2009 study by Dzhugashvili et al found use of clips significantly improved the ability to delineate the cavity.[13] They

tracked the interobserver variability of the cavity contours made by 4 radiation oncologists in 40 lumpectomy patients with and without clips. The conformity index, or ratio between overlapping volume and total delineated volume, improved by 16% (from 49%-65%) when clips were used in the cavities.

Some surgeons even elect not to clip margins because identical clips are used for hemostasis, which is the clipping of blood vessels to stop blood flow and thereby prevent inadvertent bleeding during surgery as well as angiogenesis of cancer cells. The rationale behind this method is that if clips for hemostasis are identified, they can be roughly approximated as the location of the tumor bed. Clip placement has been shown to provide favorable target contour accuracy, especially in the setting of oncoplastic surgery, but there are no data to support improved local control. Cosmetic outcomes may be improved with enhanced tumor bed delineation in patients receiving WBI or PBI.[14] It is also reasonable that less tissue may be removed during re-excisions, although no studies to date have been conducted on this topic to the knowledge of the authors of this review.

Shortcomings of surgical clip guidance

Although many studies have validated the efficacy of using surgical clips to improve delineation of postoperative tumor cavity margins, shortcomings exist with the standard of care. In irradiation planning, accuracy of tumor bed delineation is critical for accelerated partial breast irradiation (APBI) or the additional boost after WBI. Radiation oncologists' confidence in their contour of the cavity is crucial for efficacy. If the cavity cannot be clearly delineated based on the markers placed during lumpectomy, radiation oncologists have reported skipping the boost altogether.[15] In other cases, a poorly defined tumor bed may preclude the patient from receiving APBI, the preferred treatment option for reduced overall treatment time, commitment, and cost.[16]

The precision of using surgical clips as references for cavity delineation can be evaluated by the variability in contours. Wang et al analyzed the variability among radiation oncologists in delineating the postsurgical tumor bed using clips.[17] Five or more surgical clips were placed in the TB of each lumpectomy patient, and physicians delineated the TB on the end expiration CT scan. Contour variability was represented by the dice similarity coefficient (DSC), which is the spatial overlap between contour volumes, ranging from 0 (no overlap) to 1 (perfect overlap). In tumor beds receiving 5 to 6 clips, DSC_{intra}% was 86.1% and DSC_{inter}% was 73.5%. Furthermore, intraobserver variability was 6.24% and interobserver variability was 23.5%.[16] Wang et al concluded that the current state of surgical clips for tumor bed delineation produces high variability in TB contouring, which will subsequently cause geographic misses of the primary tumor during radiation after surgery.[17] Such variance poses a threat to the quality of care for the patient.

Esserman et al identified a couple of modalities for ligation clip migration on breast tissue.[18] Clips can move by simple migration in fatty tissue. When the clip is placed on fatty tissue, it has the potential to move within the breast. In addition, hematoma and seroma formation may prevent the clips from firmly gripping onto the tissue, causing them to dislodge and float in the cavity. Demircioglu et al identified an important implication of clip migration.[19] Clip movement was evaluated in 121 female breast cancer patients post breast-conserving surgery. All patients received surgical clips to mark tumor bed margins, which were used for radiation therapy planning. The evaluation was completed at the first radiologic control examination, 6 months after the last radiation therapy session. Clip displacement was quantified as the distance between the surgical scar center and the center of area delineated by the clips. On cranial-caudal view, displacement was seen in 32.2% of cases, ranging from 11 to 56 mm (mean 24.38 mm), and on mediolateral oblique projections, displacement in 64.5% of cases ranged from 11 to 66 mm (mean 24.42 mm). Demircioglu et al suggested that the current state of clips may be unreliable for tumor bed delineation, warranting an alternative solution.[19] Other studies further corroborate the issue that seroma formation does not match well with surgical clips at the time of planning CT, resulting in insufficient dose coverage with conventional boost fields.[20] The usage of alternative fiducial markers has shown less variable interphysician delineation of the seroma cavity and improved radiation therapy target volumes.[14]

Alternative solutions for radiation therapy planning guidance

In addition to the more common approaches described earlier, some breast surgeons use alternative markers. These include gold fiducial markers, implantables, and liquid-based fiducial markers.

Gold fiducials

In addition to its wide usage in oncologic operations of other areas in the body, gold fiducial markers are another alternative to mark the lumpectomy cavity. Gold fiducials have been validated for use in planning APBI[21] as they improve interobserver accuracy in tumor bed delineation.[22] They may be attached with a needle or directly sutured onto the margin walls. With a variety of shapes and sizes (spherical, cylindrical, linearized coils), the tumor bed marking can be personalized for the individual patient based on their cavity size. They are distinct in shape from clips used for blood vessel occlusion, which prevents confusion when contouring the tumor bed from

the CT scan during radiation therapy planning. To mitigate migration, some companies have designed gold fiducials that are coil-shaped or have microabrasions to improve grip onto tissue. Clinicians have reported that gold fiducials are more readily visible than titanium clips on standard megavoltage imaging electronic portal imaging devices as well as kilovoltage (KeV) x-rays,[21] whereas designs with a hollow core reduce imaging artifacts. Gold fiducials produce greater image artifacts compared with solid carbon or polymer-based markers, materials that are not yet approved for clinical use.[23] Pirlamarla et al demonstrated that placement of gold fiducials improve seroma cavity visualization compared with placement of surgical clips by the surgeon.[24] Still, if the optimal method to attach the fiducial marker is by suturing, this adds extra time and steps to the workflow of surgeons. Moreover, the fiducial markers appear on the postoperative CT scan as uniform points in a 2-dimensional space, similar to how clips mark the margins, so physicians will encounter many of the same tumor cavity delineation issues associated with titanium clips at 6 times the cost.

Implantables

BioZorb (Hologic) is an implantable 3-dimensional (3-D) bioabsorbable marker used primarily for tumor bed volume (TBV) identification during postoperative radiation planning.[25] BioZorb includes a coil-like structure that fills the cavity postoperatively and is designed to be absorbed by the body within a year of placement. The bioabsorbable coil contains 6 titanium clips distributed evenly throughout the coil. This allows for long-term 3-D visualization of the surgical site, allowing for a more in-depth visualization of the surgical sites during future procedures or through imaging. The aim of the coil design with adequate free space is to allow for tissue in-growth during the healing process. Thus far, the medical community has had mixed responses on the utility of such devices in the space of breast-conserving therapy.[26]

Studies examining the efficacy of BioZorb examined reductions in TBV in patients receiving radiation therapy for breast cancer after device implantation. Researchers conducted a retrospective case-control comparison of TBVs generated by Pinnacle3 (Philips Healthcare) treatment planning software for breast cancer patients involved in breast-conserving procedures, assessing statistically significant differences with and without placement of the device. Surgical pathology reports were used to calculate tumor evaluation volumes (cubic volume generated by the product of pathologic length, width, and depth measurements of excised specimens) after breast-conserving surgery. When comparing TBVs between patients similarly treated with or without a 3-dimensional bioabsorbable marker, device (BioZorb) placement presented significantly smaller TBVs when the tumor excision volumes (TEVs) were statistically similar. The mean TEVs were measured at 102.7 cm^3 with the device and at 103.2 cm^3 without the device, and the mean TBVs for the same groups were measured to be 27.5 cm^3 and 40.1 cm^3, respectively ($P = .001$).[25] The researchers involved in the study acknowledged the lack of prior art in the space validating the use of bioabsorbable marker placement in postoperative radiation therapy at the time of publication, but remained assured of the fact that their study provided further support for the use of such devices in breast-conserving RT planning. Although the study does show a statistically significant difference in TBV between the respective cohorts, further prospective studies at larger institutions with larger potential sample sizes will be necessary to fully validate BioZorb's role in reduction of TBV with respect to TEV.

Several studies focus on BioZorb's role in oncoplastic procedures in which, in addition to tumor removal, patients are concerned about the esthetic outcomes of the procedure.[26,27] Because oncoplastic reconstruction typically occurs immediately after lumpectomy and uses skin and fat tissue to move and hide the glandular defects that were a result of the tumor and lumpectomy,[26] the procedure obscures the original tumor cavity. As a result, precision is lost, and radiation oncologists are less confident in contouring the cavity and planning boost coverage. BioZorb has been demonstrated to reduce both the CTV and PTV boosts on average by 5.9 Gy and 13.4 Gy, respectively, during oncoplastic cases, reducing irradiation of breast tissue. However, there was an increase on average of ~2.6 Gy in ipsilateral lung irradiation.[27]

Concerns exist regarding breast firmness with BioZorb. In a study investigating 89 patients who underwent lumpectomy or a breast wide re-excision for margins at the time of BioZorb placement, the implantable continued to be palpable on clinical breast examination in 63.6% of patients at a follow-up of 1.1 years.[28] The device remained palpable on examination for up to 2.8 years. In addition, a clinician ordered additional imaging after palpating a mass because he/she was unaware that the mass was the BioZorb in 8.8% of patients. This is an issue for patients who may associate a palpable breast mass with feelings of anxiety and discomfort. For the 22 patients who underwent reoperation in this study, only 1 patient had the BioZorb removed due to discomfort. This points toward the need to counsel patients with regard to possible palpable masses with BioZorb as opposed to changing the design to address rare cases of discomfort.

Liquid fiducial markers

Liquid-based fiducial markers, originally used as spacers for prostate cancer, have been repurposed as an approach to tumor bed delineation in the field of breast cancer. These markers, which have recently been repurposed as an approach to tumor bed delineation in the field of breast cancer, allow the radiation oncologist to observe an outlined cavity volume that aids with contouring during planning CT. Target volume is adjusted to maximize

coverage to ionizing radiation, at the expense of irradiating healthy breast tissue.[29] It is advantageous to localize the area at which RT is targeted with the optimization criteria of maximizing the amount of cancerous tissue irradiated while minimizing exposure of healthy tissue. Novel liquid tissue markers such as BioXmark (Nanovi) have shown to better visualize the cavity for radiation localization.[30] The BioXmark hydrogel marker is composed of sucrose acetate isobutyrate with an electron-dense analogue and an ethanol component to increase viscosity during diffusion of the liquid after application.

Visible on magnetic resonance imaging, CT, and fluoroscopy, BioXmark has a life span of several months and provides a clearer modality for observation, thereby reducing interobserver variability compared with delineation with surgical clips.[30] These results are mirrored in an analogous liquid fiducial marker, TraceIT (Augmenix), that is applied to the breast cavity after a lumpectomy.[31] Composed of polyethylene glycol, this radiopaque hydrogel marker increased the conformity index by a factor of 0.54 with respect to CT and 0.83 with respect to magnetic resonance imaging compared with standard surgical occlusion clips. Similar to BioXMark, a lower interobserver variability was reported.

Studies on both technologies noted that after CT scans for treatment planning, manual processing of the 3-D structures was necessary due to liquid markers having similar density to that of physiological structures, such as those defined by mammary ducts. However, Ciernik and Greiss also noted that compared with metal-based fiducial markers, hydrogel markers lead to less image distortion due to a lower degree of beam-hardening artifacts.[29] Toxicity was not observed in either study, but the resorbed BioXmark marker mimicked microcalcifications on radiographs and could be misinterpreted as a relapse or intraductal carcinoma.[29] The value of visualization of the tumor cavity with hydrogel fiducials has been demonstrated in a recent case report, in which cavity shrinkage with boost radiation was not paralleled by a corresponding reduction in tissue volume as indicated by hydrogels injected in close proximity (1-3 cm) from the seroma cavity - it was chosen to use the original planning CT to define a wider boost target volume for the cavity.[32]

Conclusion

This review has assessed the current standard and fiducial marker technologies available to aid RT planning. Regarding the ability to fully delineate the margins of tumor bed cavities, most technologies discussed proved insufficient, as summarized in Table 1.

Commonly used by surgeons, titanium clips appear as distinct points on CT, requiring radiation oncologists to draw inferences about the tumor cavity volume. As

Table 1 Comparison of technologies for tumor bed cavity marking

Technology	Cost	Timing of device placement	Safety	Tumor bed delineation	Interobserver variability	Absorbed	Logistic considerations
Titanium clips	Low	After lumpectomy	Low risk	Point markers, no precise boundaries	High (conformity index = 65%)	No	-Clip migration
Liquid fiducial markers	High	After lumpectomy	Low risk	Outlines entire tumor cavity, visible by CT	Lower in comparison to clips (higher conformity index)	Yes (TraceIT)	-Manual processing of 3-D structures -May mimic microcalcification on radiographs
Gold fiducials	Medium	After lumpectomy	Low risk	Point markers, no precise boundaries	Lower in comparison to clips	No	-Microabrasions help mitigate migration -Variety of shapes to fit individual cavities
Implantables (e.g., BioZorb)	High	After lumpectomy	Moderate risk	Approximates tumor cavity boundaries	High	Spiral absorbed in 1 y	-Smaller TBV -Difficulty in oncoplasty

discussed, such guesswork has proved widely imprecise and inaccurate, with high interobserver variability and a high probability of missing significant portions of tumor cavity during radiation boost therapy. Gold fiducial markers also presented the same issues in regard to tumor bed cavity delineation, but with the added benefit of mitigated migration risk with microabrasive features. Additionally, implantable devices like BioZorb proved insufficient in accurately delineating tumor bed volume as tumor bed volumes delineated were significantly smaller than mean TEV values.

The most effective device for delineating tumor bed cavities was found to be liquid fiducial markers. Namely, the ability of the liquid fiducial markers to be applied throughout the entire tumor cavity volume proved essential in the device's higher ability to display tumor bed margins on CT without interpolations from radiation oncologists. Liquid fiducial markers have limitations, primarily reabsorption that can rarely be mistaken for microcalcifications, but minimize the challenges of using surgical clips or implantables. Liquid fiducial markers allow visualization of the entire cavity and minimize interobserver variability compared with other solutions. Future solutions in this space should consider modifying liquid fiducial markers and other technologies to improve radiation oncologists' ability to consistently delineate the tumor bed, thus optimizing irradiation of the breast tissue in PBI and WBI plus boost therapies to improve clinical outcomes and patient cosmesis.

Acknowledgments

We would like to thank the Center for Bioengineering Innovation and Design, Department of Biomedical Engineering at Johns Hopkins University, and the Johns Hopkins School of Medicine faculty for providing guidance and financial support for the research contributing to this review.

Supplementary materials

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.adro.2021.100848.

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