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Systematic review

Tumor bed delineation for external beam accelerated partial breast irradiation: A systematic review

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ABSTRACT

In recent years, accelerated partial breast irradiation (APBI) has been considered an alternative to whole breast irradiation for patients undergoing breast-conserving therapy. APBI delivers higher doses of radiation in fewer fractions to the post-lumpectomy tumor bed with a 1–2 cm margin, targeting the area at the highest risk of local recurrence while sparing normal breast tissue. However, there are inherent challenges in defining accurate target volumes for APBI. Studies have shown that significant interobserver variation exists among radiation oncologists defining the lumpectomy cavity, which raises the question of how to improve the accuracy and consistency in the delineation of tumor bed volumes. The combination of standardized guidelines and surgical clips significantly improves an observer's ability in delineation, and it is the standard in multiple ongoing external-beam APBI trials. However, questions about the accuracy of the clips to mark the lumpectomy cavity remain, as clips only define a few points at the margin of the cavity. This paper reviews the techniques that have been developed so far to improve target delineation in APBI delivered by conformal external beam radiation therapy, including the use of standardized guidelines, surgical clips or fiducial markers, pre-operative computed tomography imaging, and additional imaging modalities, including magnetic resonance imaging, ultrasound imaging, and positron emission tomography/computed tomography. Alternatives to post-operative APBI, future directions, and clinical recommendations were also discussed.

Breast-conserving therapy (BCT) consists of wide local excision followed by radiation therapy (RT) to the whole breast. The efficacy of BCT in the treatment of early-stage breast cancer has been established through multiple randomized trials [1–6]. Three of the largest trials with twenty-year follow-up demonstrated equivalent survival between patients who received BCT compared to mastectomy [3–5]. The addition of boost irradiation to the tumor bed after whole breast irradiation has been shown to further improve local control [7]. As radiation morbidity is directly related to irradiated volume [8], limiting RT treatment volume can expectedly decrease late toxicity. Accelerated partial breast irradiation (APBI) delivers a whole course of post-operative RT to the lumpectomy tumor bed, whereas conventional RT after BCT is delivered to the whole breast with a few more fractions of the radiation given to the tumor bed as a boost. APBI has gained popularity in recent years. Its ability to limit RT exposure to normal tissues and its shorter treatment course are some of the reasons that make it attractive for both clinicians and patients with early-stage breast cancer suitable for APBI treatment. The rationale for this strategy is that most local recurrences appear close to the tumorectomy cavity [9]. Pathologic studies have also shown that tumor cells rarely extend 4 cm beyond the index lesion [10]. These studies suggest that RT offers the greatest local control benefit when doses are directed to the tumor bed.

There are multiple delivery methods for APBI [9,11–13] and external beam RT (EBRT) is a popular technique utilized due to its non-invasive nature and availability. In small series, external beam APBI (EB APBI) has shown adequate efficacy and limited toxicity at short-term follow-up [11,14]. A larger planning target volume (PTV) is also used in EB APBI. The clinical target volume (CTV) is derived from adding a margin of usually 1.5 cm around the tumor bed volume (TBV). Then, an additional 0.5–1.0 cm margin is added to obtain the PTV. For interstitial brachytherapy APBI, however, no additional margin around the CTV is required; therefore the CTV is the PTV. Depending on the technique used, the

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coverage of the PTV and thereby the irradiated volume varies considerably. The irradiated volume in IORT is in general small, with the dose mainly delivered to the surface of the surgical tumor bed, which then attenuates to deliver lower doses to the surrounding tissue. As the tumor is often eccentric in the lumpectomy specimen, treatments given at the time of surgery can lead to insufficient dose delivery to the high-risk region (Fig. 1) [15]. This is typically not the case for APBI delivered with EB or with interstitial brachytherapy, as with these techniques conformal RT can be delivered to the entire high-risk region.

Given that APBI delivers conformal RT to the tumor bed with a small margin, defining the post-surgical tumor bed accurately for treatment planning and delivery is essential in achieving treatment efficacy. However, several studies have shown that interobserver variation is common among radiation oncologists in defining the lumpectomy cavity [15–17]. This review sets its scope to EB APBI only. We will discuss four general methods investigated to improve consistency in tumor bed definition during EB APBI planning, including the use of standardized guidelines, surgical clips or fiducial markers, pre-operative computed tomography (CT) scans, and additional imaging modalities in treatment planning, including magnetic resonance imaging (MRI) and ultrasound (US) imaging. We will also discuss recent reports of bypassing the uncertainty of tumor bed delineation by applying EB APBI to the intact tumor prior to lumpectomy, and future directions and clinical recommendations.

While we present a comprehensive overview of the current state of tumor bed delineation for APBI with this manuscript, a systematic review was performed specifically for the section in evaluating methods in improving interobserver variability. We searched for English-language papers published from January 2005 to May 2012. Studies comparing clinical methods in the evaluation of interobserver variation in tumor bed delineation including guidelines, fiducial, and imaging were included. Using PubMed, the search was completed in May 2012. The search strategy was (target[tw] or volume[tw] or tumor bed[tw]) AND breast[tw] AND radiotherapy[tw] (delineation[tw] or contour[tw]), which identified 74 studies. While many of the studies supported the theme of improving tumor bed delineation with clinical tools, 14 described interobserver variations, and 8 provided a direct comparison of interobserver variation with and without the proposed clinical strategy. These 8 studies were detailed in this manuscript.

Variability in tumor bed delineation

Accurate delineation of the target volume is a prerequisite of conformal RT and is critical to achieving long-term local control

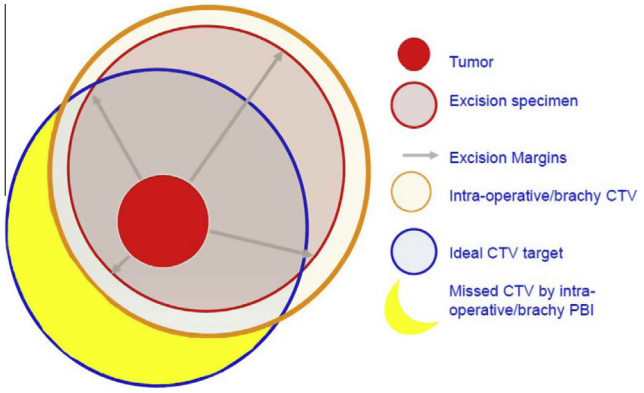

Fig. 1. From Bartelink et al. [46]. Illustrations of breast tumors are often eccentric, which may lead to variation in resection margins addressed by brachytherapy or intraoperative radiotherapy (IORT). CTV = clinical target volume, PBI = partial breast irradiation.

for APBI. However, multiple studies have reported significant interobserver variation in delineating post-lumpectomy cavities, indicating observers' inability to accurately and consistently define treatment target volumes. It is important to note that many of the studies to date looked at variability in tumor bed contours for boost irradiation and are being used as a surrogate for APBI tumor bed definition in this review. To quantify interobserver discrepancies, in addition to volumetric analysis, investigators commonly use the following parameters in their studies (Fig. 2):

(1) Conformity index (CI): the ratio of the overlapping volume and the encompassing total delineated volume of the structure of interest, ranging from 0 to 1, with 0 indicating no overlap in volume and 1 implying perfect agreement. When evaluating smaller volumes, such as TBV, a low CI is less relevant in indicating inconsistency, compared to a low CI when evaluating larger volumes, such as CTV and PTV.

(2) Center of mass displacement (COMd): the variation in distance between the centers of two delineated structures. A zero COMd signifies that the delineations are centered at the same position but does not mean the structures are the same.

(3) Standard deviation (SD): the standard deviation of the variations in distances among observers' delineations. This value describes the distribution of interobserver variation around the mean.

Table 1 shows a comparison of studies demonstrating poor interobserver consistencies in tumor bed delineation. Struikmans et al. compared the CI of target volumes for boost irradiation using eighteen patients' treatment planning CT scans [18]. The authors found high interobserver variability (CI = 0.56), which was enhanced by the relatively small boost volume. Similar findings were demonstrated by Landis et al., reporting a mean overlap of 57% for the contoured lumpectomy cavity and a median COMd of 0.69 cm between four radiation oncologists in patients with low post-surgical cavity clarity [15]. These clarity and volume effects on observer discrepancies were echoed by investigators at the British Columbia Cancer Agency and the Netherlands Cancer Institute [16,19]. To evaluate multi-institutional and multi-observer variability, Li et al. compared the contoured target volumes of nine radiation oncologists from eight institutions. Despite the clearly visible seroma and surgical clips in the two patients in the study, the authors found that the delineated size (cm^3) of the lumpectomy cavity varied by an average of 36% and the mean COMd was 0.23 cm [20]. From the above studies, we find that there are clinically relevant differences between observers in lumpectomy cavity delineation. Discrepancies in contouring target structures can undermine the precision of conformal RT. In order to ensure adequate RT delivery through APBI to areas at risk, it is crucial to establish consistency in target volume delineation. Furthermore, as the long-term effectiveness of APBI is still being evaluated through multiple clinical trials [21–24], discrepancies in target volume definitions by different investigators may negatively influence trial results.

Lumpectomy cavity closure

Before examining clinical strategies in improving variability in target delineation for EB APBI, it is important to briefly discuss the how surgical techniques may influence an observer's ability in contouring the post-surgical cavity and its implication. During a lumpectomy, surgeons traditionally elect to use either a superficial or full-thickness closure when sealing the cavity. With superficial closure, only the superficial aspect of the cavity is closed, allowing the formation of a seroma to prevent deformation of

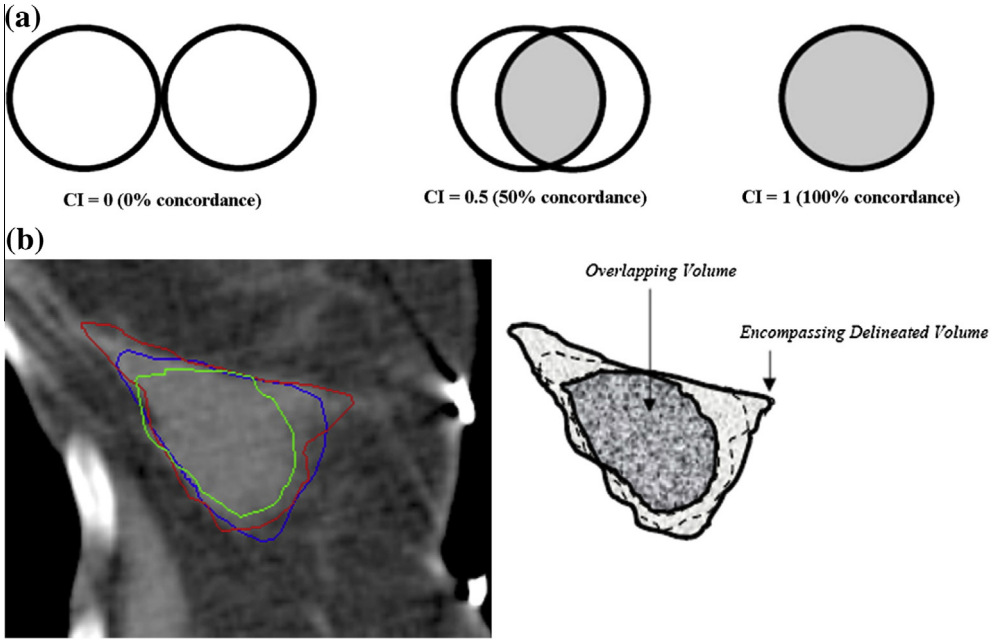

Fig. 2. From Petersen et al. [16]. (a) Illustration of the conformity index (CI) defined as a ratio of overlapping volume to encompassing delineated volume: representations of 0%, 50%, and 100% concordance. (b) Case demonstrating variation in seroma contouring by three observers. CI = conformity index.

Table 1
Studies demonstrating poor interobserver consistencies in tumor bed delineation.

Publications	Target volumes	Number of patients	Observers	Conformity index (CI)	Center of mass displacement (COMd)	Factors reducing consistency
Struikmans et al. [18]	Boost target volume, breast	18	5 (2 radiation oncologists, 2 registrars, 1 radiologist)	CI boost: 0.56; CI breast: 0.87	–	Smaller target volume
Landis et al. [15]	Lumpectomy cavity	33	4 (radiation oncologists)	0.57	0.69 cm	Smaller lumpectomy volume
Petersen et al. [16]	Seroma volume	30	3 (radiation oncologists)	0.61	–	Smaller seroma volume, low clarity score, tissue stranding, proximity to the pectoralis, dense breast tissue, benign calcifications
Yang et al. [19]	Seroma volume	19	2 (trainees, checked by a radiation oncologist)	0.61	–	Smaller seroma volume, low clarity score
Li et al. [20]	Lumpectomy cavity, boost, breast, nodal volumes, and chest wall	3	9 (radiation oncologists from 8 institutions)	As low as 0.10	0.23 cm	–

the breast. A full-thickness closure consists of repositioning of the surrounding breast tissue and suturing the deep and superficial layers, preventing the development of significant seroma [25,26]. There is a paucity of data on the influence of surgical closure techniques on EB APBI treatment planning. It can be hypothesized that superficial closure may lead to a better-delineated cavity as a well-visualized seroma has been shown to decrease interobserver variations [19,27], nevertheless, it may also lead to a larger treatment volume and greater late toxicity effects. However, with full-thickness closure, the surgical clips may be displaced with the approximation of the surrounding breast tissue and not correlate with the true extend of the cavity. In a recently published single institutional experience, Shaikh et al. did not find statistically significant difference in mean cavity visualization scoring (CVS) (Smitt et al., 1 = no visible cavity, 2–4 = heterogeneous cavity with indistinct, distinct, or clearly defined margins, 5 = homogenous cavity with clearly defined margins [28]) or normal tissue dosimetric endpoints between 29 patients who underwent superficial closure and sixteen patients who underwent full-thickness closure [29]. A higher percentage of patients who underwent superficial closure had CVS scores >2 (79% vs. 63%). The small patient numbers in each cohort and its retrospective nature are the limitations of the study.

Another important trend to consider in tumor bed delineation for post-BCS EB APBI is the increasing utilization of oncoplastic reconstructions at the time of BCS to achieve better cosmetic outcome, during which the position of the tumor bed may be shifted due to breast tissue rearrangement, the surgical cavity may not represent the original tumor volumes. A recent retrospective study showed that in a cohort of 25 patients who underwent oncoplastic reconstruction with a minimum of four surgical clips placed at the time of BCS, 73% of patients had a final tumor bed extending beyond the original breast quadrant where the tumor was located or was completely relocated to a different region [30]. Identifying the tumor bed for EB APBI after oncoplastic surgical remodeling can be difficult, and the displacement of the tumor bed can lead to a larger treated volume due to the segmentation of the TBV into different locations in the breast [31]. Whether certain surgical technique should be

considered as one of the exclusion criteria for EB APBI is an area of debate and requires more evidence.

Methods for improving delineation consistency

Different approaches in improving delineation uniformity have been tested and used by various groups. Overall, these studies can be separated into four categories: utilization of standardized guidelines, surgical clips and/or fiducial markers, pre-operative CT scans, and additional imaging modalities in treatment planning. Many investigators used more than one of the above techniques in their studies. The results and limitations of each method are discussed in this section.

Standardized guidelines

Given that the ability to identify the surgical cavity after breast-conserving surgery (BCS) may vary depending on the experience of the radiation oncologist, investigators have tested the impact of implementing standardized guidelines on consistency in lumpectomy cavity contouring. One of the first studies using an institutional protocol in contouring in breast cancer took place at the British Columbia Cancer Agency [17]. Based on prior studies in patients with bladder cancer and prostate cancer [32,33], the authors tested the hypothesis that using precise contouring protocols would reduce delineation variability. Eight radiation oncologists were asked to contour the post-operative seroma on the treatment planning CT scans of five patients. The observers were separated into two groups: one group contoured with guidelines (the "trained" observers) and the other group did not (the "untrained" observers). The guidelines defined the seroma target volume as the surgical cavity after removal of the primary tumor, specifying that breast tissue stranding should not be included in this volume. The guidelines then specified the CTV and PTV expansions, with the CTV defined as the seroma volume plus a 1 cm expansion that is then trimmed to 5 mm from the skin and breast–chest-wall interface. The PTV was defined as CTV plus a 1 cm expansion. The authors found the contours of the seroma volume, CTV, and PTV of the "untrained" cohort were consistently and statistically significantly larger than the "trained" cohort. During the second phase of the study, all eight observers were given guidelines for contouring on five new patients and the differences in volumes between the observers were no longer significant, demonstrating improvement in consistency among radiation oncologists in volume delineation when they were asked to follow specific guidelines. This study was limited by the lack of evaluation of spatial conformity, as only volumetric data was tested. No patients in the study had clips placed in the surgical cavity.

More recently, van Mourik et al. of the Netherlands Cancer Institute reported the findings of their multi-institutional study comparing thirteen radiation oncologists' breast target volume delineations of eight patients [34]. The authors observed significant volumetric and spatial interobserver variation in CTV (mean CI = 0.53; SD = 0.6 cm), even with the use of delineation guidelines, and the presence of clips or seroma reduced interobserver variation. The guidelines used in this study asked the observers to delineate the original tumor bed or excisional cavity. If there was no visible seroma, the observers were asked to contour the original tumor location using all available pre-operative information to delineate the tumor bed. If there was a visible seroma, the observers contoured the excisional cavity to include the seroma and the seroma wall. The CTV was defined as a 1.5 cm expansion around these contours and excluded skin, muscle, ribs, and lung. The PTV was then created with a 0.5 cm expansion of the CTV. The authors found delineation differences between observers in the contoured volumes and the locations of the targets, showing that interobserver variation was partly caused by differences in radiation oncologists' opinions on what should be considered as the target volume even while using guidelines.

These studies suggest that the presence of standardized delineation guidelines may reduce differences in target delineation among radiation oncologists. However, considerable variation can still exist. While standardized guidelines remove some ambiguity in target interpretation, subjective determination of the location of the post-surgical cavity nevertheless contributes to interobserver variability. Additional strategies should thus be considered to improve consistency.

Surgical clips and fiducial markers

Many previous studies have advocated the use of surgical clips in localizing the lumpectomy cavity and guiding coverage for boost irradiation to the tumor bed as part of BCT [35–38] (Table 2 includes examples of studies demonstrating the utility of surgical clips.). As reported by van Mourik et al., the presence of visual landmarks, such as surgical clips, within the lumpectomy cavity significantly improved observer consistency in tumor bed delineation (in patients with surgical clips, lowest CI = 0.47; in patients without surgical clips, lowest CI = 0.19) [34]. While the authors also reported that post-surgical seromas could reduce observer discrepancies in their study, seroma formation heavily depends on surgical techniques and its volume has been shown to be dynamic during RT [39]. Therefore, surgical clips are considered more reliable visual landmarks and have been tested as surrogates for surgical cavities [40].

In 2010, Dzhugashvili et al. at the Institut Gustave Roussy investigated whether the placement of surgical clips facilitated radiation oncologists in delineating the lumpectomy cavity in the setting of APBI [27]. In this study, two radiation oncologists prospectively evaluated 100 patients who had undergone lumpectomy with four surgical clips placed at the time of surgery within the lumpectomy cavity at the upper, inner, outer, and lower surgical margins. The physicians delineated three CT slices of the cavity, with surgical clips defining the superior and inferior slices, and the CT slice of the middle of the cavity did not include a surgical clip. Each lumpectomy cavity was also graded using a CVS system initially proposed by Landis et al. [15]. A CVS of 1–2 represented a poorly defined cavity, 3 indicated an intermediately defined cavity, and 4–5 indicated a well-defined cavity. The authors found surgical clips significantly improved clinicians' ability to visualize the lumpectomy cavity (29% of patients without surgical clips and with CVS scores $\geqslant 3$ vs. 75% of patients with surgical clips and CVS scores between $\geqslant 3$). In another study, the authors investigated whether surgical clips could

Table 2
Studies showing utility of surgical clips in target localization.

	Number of patients	Radiotherapy plan	Results
Krawczyk et al. [38]	25	Tangential fields planned with and without clips visible	Surgical clips prevent underdosing of the lumpectomy cavity, especially if it is on the medial/lateral border of breast tissue
Kovner et al. [37]	40	Boost of the lumpectomy cavity using surgical scar vs. clips	1/4 of the lumpectomy cavity was missed without clips; clips also reduced the total target volume
Benda et al. [35]	30	Boost of the lumpectomy cavity using surgical scar vs. clips	Significant underdosing of the lumpectomy cavity without clips: 49% of patients received <90% of prescribed dose

improve interobserver variation by examining the lumpectomy cavity contours of four radiation oncologists (two experienced physicians, two trainees) of 40 patients [41]. CTV in this study was defined as surgical clips plus remodeled breast tissues (mobilized glandular tissues adjacent to the tumor bed after wide local excision). The authors found the CTV CI to be relatively low for both the trainees and experts (0.48 and 0.53, respectively). When only CT slices containing surgical clips were assessed, the CI improved for both groups of radiation oncologists (0.55 for trainees and 0.65 for experts). The same improvement was demonstrated with COMd. When the entire CTV was evaluated, the COMd ranged from 0.26 cm to 0.35 cm and improved when only CT slices containing surgical clips were evaluated (0.18–0.3 cm). The authors concluded that surgical clips improved the accuracy of lumpectomy cavity delineation, since the CI between observers was increased by 16% (from 49% to 65%).

A limitation of surgical clips is that they may not be easily identified on portal images. Because of this, gold fiducial markers have been used because they have the advantage of better visibility, which allows for tracking the lumpectomy cavity during RT through image guidance [42]. Shaikh et al. recently investigated whether gold fiducial markers would improve interobserver accuracy in surgical cavity delineation in the setting of APBI [43]. In the study, twenty-two patients were enrolled and eleven of them received four to six gold fiducial markers during lumpectomy. The post-lumpectomy cavities, CTV, and PTV were contoured independently by 3 radiation oncologists. Before defining the tumor bed, the physicians were required to give each tumor bed a CVS according to guidelines established by Smitt et al. [28]. The authors found that a physician's ability to visualize the cavity significantly improved with fiducial markers (mean CVS = 2.5 without markers vs. 3.6 with markers). Also significantly improved, as compared to patients without gold fiducial markers, were the mean CTV CI (0.43 without markers vs. 0.70 with markers; $p < 0.0001$) and COMd (0.56 cm vs. 0.24 cm; $p < 0.001$), indicating that physicians were able to identify the lumpectomy cavity more consistently.

Although visual landmarks, such as surgical clips and gold fiducial markers, are able to improve consistency in lumpectomy cavity delineation, their accuracy in representing the original tumor site is a matter of debate. Yang et al. recently reported that surgical clips are not always consistent with the tumor bed's edge and therefore, may not accurately represent the original tumor site. The authors demonstrated that the seroma on CT scans can extend beyond clips by 0.5 cm [44]. Similar findings were reported by Goldberg et al. [45], who found that the lumpectomy cavity on CT scans exceeded the clips by 0.7 cm medially. These results suggest that the standardization of clip placement should be considered as an important part of surgical protocol to ensure RT accuracy.

It is important to keep in mind that each surgical clip marks only a single point within the surgical bed, requiring observers to interpolate the border of the cavity, which can contribute to inaccuracy in target delineation. In some cases, the clips may be placed beyond of the edges of the tumor bed, as surgeons may manipulate them into more structurally stable tissue. For gold seeds, the standard gold seed applicator buries the seed into the tissue, rather than placing it at the immediate edge of the tissue. Furthermore, surgical clips and fiducial markers may help define the border of the excised tissue, but they do not give us any information on the distance of the tumor from the border, as the location of the tumor within the excised specimen varies among patients, leading to variable margins [46].

Pre-operative CT scan

The use of a pre-operative CT scan in the RT treatment position matched with a post-operative treatment planning CT scan to guide clinicians in identifying lumpectomy cavities was first described by Kirova et al. [47] The pre-surgical CT scan was performed 1 week prior to BCS with the administration of intravenous contrast and the postsurgical CT scan was performed 4–5 weeks after lumpectomy. Rigid image registration was then performed, matching different types of anatomical structures. The primary tumor was seen and delineated on the pre-operative CT scan (gross tumor volume [GTV]), and a region including surgical clips and the GTV was then contoured on the post-operative CT scan and was defined as the CTV. While the authors demonstrated the feasibility of identifying post-lumpectomy treatment volumes after registration of the pre- and post-operative CT scans, the influence of the pre-operative CT on delineation was not analyzed in this study. More recently, the use of deformable registration of pre- and post-operative CT scans has been shown to add value in defining the post-operative tumor bed, especially in the setting of oncoplastic surgery, where the breast tissue can be remodeled extensively [48].

In a multi-institutional study, Boersma et al. investigated whether using contrast-enhanced pre-operative CT scanning in combination with a standardized delineation protocol could decrease interobserver variation in boost irradiation target volumes. The CT images of 26 patients enrolled in the study were contoured by five radiation oncologists [49]. First, the observers contoured the TBV and the CTV (1.5 cm expansion of TBV) on the post-operative planning CT scan and then, they contoured the tumor on the pre-operative CT scan (GTV). The observers were presented with anatomy-matched scans of the pre-operative CT showing the GTV and the post-operative planning CT showing the TBV and CTV. With pre-operative volume data, the observers were asked to adjust the TBV and CTV delineations for each patient as needed. The authors found that using pre-operative CT as part of CTV delineation resulted in smaller mean boost-CTVs (a decrease from 42 cc to 36 cc; $p = 0.005$) and a significant but modest reduction of the COMd of the CTV delineations (from 1.1 cm to 1.0 cm; $p < 0.001$), without significant change in CI and SD. The authors concluded that incorporating pre-operative CT scans in tumor bed delineation, in addition to standardized guidelines, resulted in a significant reduction of interobserver variation. Interestingly, the authors reported a low mean CI in the study (0.36), which was attributed to ambiguity in standardized guidelines regarding excision cavity delineation. As the CI is highly dependent on the absolute volume, a low CI value could also be attributed to the small volumes reported in the study.

Although the addition of pre-operative CT scans to standardized guidelines in tumor bed delineation appears to further reduce interobserver discrepancy, there are limitations to this method. First, not all breast tumors can be reliably and easily identified on the pre-operative CT scan. In the multi-institutional study cited above, one observer had difficulty identifying the correct GTV on three patients. Second, because of different surgical margins used, the relationship between the tumor volume and TBV may vary. Third, due to post-surgical breast changes, it can often be difficult to reliably match the pre- and post-operative CT scans through rigid registration. While the pre-operative tumor information is a good reference, it is still important to consider other techniques in helping clinicians to dependably identify the post-operative tumor bed to ensure that APBI is accurately delivered.

Additional imaging modalities

As shown in several studies, interobserver variation in lumpectomy cavity delineation on CT scan is heavily influenced by the clarity of the surgical cavity [15,27], and visual landmarks within the surgical bed improve delineation consistency [19,34]. For patients with poor seroma clarity or dense breast parenchyma, it

is particularly challenging to differentiate the tumor bed from normal breast tissue, given the lack of contrast seen on CT scans [16]. Several investigators have addressed the use of additional imaging modalities, either in conjunction with CT or direct comparison against CT for better defining the lumpectomy cavity.

Magnetic resonance imaging (MRI), ultrasound (US), and positron emission tomography (PET) are means to provide images of soft tissue definition and inflammatory changes around the surgical site, which would be useful in defining the tumor bed. Using deformable registration to guide observers in tumor bed definition is an ongoing area of research.

MR Imaging

In 2008, Whipp et al. investigated the appearances of post-operative cavities in 100 women who underwent BCS using MRI and found the cavities tend to be heterogeneous in signal, suggesting the formation of granulation tissue and that the true boundary of the surgical cavity may be outside the seroma–tissue interface. Thus, they proposed that an MRI scan may be superior to a CT scan in defining the tumor bed [50]. To investigate whether the addition of MRI to CT and surgical clips improves delineation, Kirby et al. enrolled 30 patients with 6–12 titanium clips placed in the excision cavity at the time of BCS and who underwent CT followed by MRI [51]. The lumpectomy cavity was first delineated on the CT scan and then, on the MRI at least 2 weeks later by a single observer. The MRI- and CT-defined TBVs were then fused using regions of interest corresponding to the midpoint of each surgical clip to create a single MRCT-defined lumpectomy cavity. The CTV was created by adding a 1.5 cm margin to the tumor bed. The authors found a CI of 0.54 between CT and MRCT for the tumor bed and 0.84 for the CTV, concluding that intra-observer variation in tumor bed delineation was significantly higher with the CT scan. However, the resulting clinical target volumes were sufficiently in concordance, as the expansion of the margin resulted in larger volumes and an increase in CI. Given these findings, the authors did not feel the addition of MRI to CT and surgical clips would be needed in tumor bed delineation for APBI.

More recently, interobserver variability in delineating the lumpectomy cavity using MRI and CT scans was evaluated by Giezen et al. [52]. In their study, fifteen patients underwent RT treatment planning CT scans and immediately afterward, an MRI scan was performed in the treatment position. Four observers (two radiation oncologists and two radiologists) assessed the CVS according to Smitt et al. [28] and delineated the lumpectomy cavity on each scan. Two patients did not receive surgical clips at the time of BCS and the rest of the patients had 4–6 clips placed within the tumor bed. The authors found that MRI resulted in a significantly lower CI (0.32 for MRI vs. 0.52 for CT) and higher COMd (0.11 cm with MRI vs. 0.04 cm with CT). They also found that MRI was inadequate in tumor bed localization in the setting of low CVS as surgical clip visibility on MRI was too low. The authors concluded that MRI added no further information to CT for patients with low CVS and while MRI may provide more information for patients with high CVS, it must be combined with CT/surgical clip data for optimal tumor bed delineation.

Ultrasound Imaging

In 2000, Robinovitch et al. published one of the earliest studies using 2-dimensional (2D) US in visualizing the lumpectomy cavity [53]. The authors compared surgical bed dimensions determined by US to that determined by the evaluation of plain film of 5–6 surgical clips and found measurements derived by US were significantly smaller than that derived of clips. The authors concluded that US is highly inaccurate in identifying the lumpectomy cavity. Conflicting results were found by Ringash et al., where the authors reported that US localization in lumpectomy cavities was adequate in 65% of patients and that it could be used when surgical clips are not available [54]. A major disadvantage of these studies was that no 3D imaging was used in the visualization of the tumor bed. In 2007, Coles et al. conducted a direct comparison of tumor bed delineation of 3D US co-registered with CT, 2D US and CT, surgical clips and CT, and CT alone [55]. Confirming previous findings, the authors found US (both 2D and 3D) showed a smaller lumpectomy cavity volume than surgical clips, possibly due to tissue changes at the edge of the cavity. Clips could also be pushed into the breast tissue, leading to an increased volume marked by clips. It was concluded that US, compared with the use of surgical clips and CT for localization, defines different volumes as post-surgical remodeling occurs. Interobserver consistency in lumpectomy delineation using US was evaluated at the British Columbia Cancer Agency [56]. After BCS, twenty patients underwent 3D US and treatment planning CT, and three radiation oncologists contoured the post-operative seroma on each image set. The authors found that, compared to CT alone, the addition of 3D US was associated with a higher CI in 40% of cases, especially in patients with low seroma clarity on CT alone and extremely dense breast parenchyma. Use of 3D US may be useful in improving interobserver variation in selected patients. However, if surgical clips on CT scan are considered the gold standard, US may underestimate the TBV, as demonstrated above (Table 3 summarizes the two interobserver studies for US and MRI).

PET/CT Imaging

In 2008, Ford et al. at the Johns Hopkins University [57] first used this imaging technique for lumpectomy cavity definition. Since [18F]-fluorodeoxyglucose (FDG) uptake in PET/CT has been shown to be high in areas with inflammatory cell response [58,59], the authors hypothesized that the lumpectomy cavity, due to surgery, would exhibit inflammation and therefore, result in greater FDG uptake. Enrolled in their study were twelve patients with a median time from surgery to PET/CT of 49 days. The lumpectomy cavity was contoured on the CT scan by a radiation oncologist and on the PET/CT scan by both a radiation oncologist and nuclear medicine physician. The authors found the lumpectomy cavity was visualized well on PET/CT, but the PET/CT volumes were larger than the CT volumes in all patients (median ratio, 1.68). It is unclear if the PET/CT contour is more representative of the actual extent of the lumpectomy cavity or if it is due to peri-surgical inflammation. The authors concluded that TBV would likely be overestimated using PET/CT. However, to date, there is no study evaluating interobserver variations using these imaging methods.

Alternatives to post-lumpectomy radiation

In order to eliminate issues of inaccurate lumpectomy cavity delineation and interobserver variability, trials with APBI using pre-operative EBRT followed by BCS are currently recruiting at various institutions [60,61]. At a trial at the Netherlands Cancer Institute, patients with early-stage breast cancer first undergo a 12-day course of APBI and then, the lumpectomy 6 weeks later. The extent of the primary tumor is identified on treatment planning imaging, thus eliminating the question as to what extent of the post-surgical cavity represents the primary tumor location. Although the accuracy of CT-defined tumor volume compared to MRI or US requires more investigation, a comparative study on 41 patients with early-stage breast cancer by Nichols et al. showed that the PTV delineated from pre-lumpectomy CT was consistently smaller than that delineated from post-lumpectomy CT [62]. Furthermore, the type of surgical closure technique can influence the post-operative TBV. Therefore, using pre-lumpectomy PTV for EB APBI will lead to smaller treatment volumes and possibly, improved long-term

Table 3
Interobserver studies using MRI and ultrasound imaging.

Imaging	Paper	Observers	Number of patients	Measures of interobserver consistency	Conclusions
MRI vs. CT	Giezen et al. [52]	4 (2 radiation oncologists, 2 radiologists)	15	Significantly lower CI with MRI (0.32) vs. CT (0.52); significantly higher COMd with MRI (0.11 cm) vs. CT (0.04 cm)	MRI is worse for interobserver delineation consistency. It can provide additional information for patients with high CVS but its use must be combined with CT data
3D Ultrasound (US) vs. CT	Berrang et al. [56]	3 (radiation oncologists)	20	CI improved with the use of US compared to CT in 40% of patients; US seroma clarity not affected by dense breast tissue or low seroma volume	3D US improves interobserver variation in select patients with dense breast parenchyma, small seromas, or poor CT seroma clarity

Table 4
Standards employed in ongoing trials of external beam partial vs. whole breast irradiation.

Publications	Imaging modality	Tumor bed delineation	Tumor bed to CTV margin (mm)	CTV to PTV margin (mm)
NSABP B-39/RTOG 0413 [24]	3D-conformal external beam, mammosite balloon catheter, and multi-catheter brachytherapy	CT ± tumor bed clips	15	10
Ontario clinical oncology group [23]	Multiple static tangent fields	CT + 6 pairs of titanium clips recommended. CT or ultrasound alone, only if seroma is visible	15	10
Danish breast cancer co-operative group [22]	3D-conformal external beam radiation therapy	CT ± tumor bed clips	15	5–8
IRMA [71]	3D-conformal external beam radiation therapy	CT + tumor bed 3–6 surgical clip	15	5
SHARE [72]	3D-conformal external beam radiation therapy	CT + 5–6 tumor bed clips	NA	15–20

cosmetic outcome. The drawback of treating patients with pre-operative RT is that there is the potential to delay definitive surgical management and that radiation can cause tissue changes that render surgery more difficult. Although a novel approach can potentially change the treatment of early-stage breast cancer, this shift in paradigm needs to be validated with the long-term outcome that has already been established for the current paradigm of BCS followed by adjuvant radiation.

Palta et al. recently conducted a dosimetric study of single-fraction pre-operative APBI by creating virtual plans for seventeen patients with unifocal stage T1 breast cancer [60]. A contrast-enhanced MRI was used for treatment planning with the preoperative tumor defined as the GTV. CTV was a 1.5 cm expansion around the GTV, and PTV was created as a uniform 3 mm expansion of CTV minus the first 5 mm of the subcutaneous tissue. The prescription dose to the PTV was 15 Gy. Compared to 27 postoperative PBI patients, the V100% and V50% were approximately 4 folds smaller in the pre-operative APBI. The authors conclude that, in addition to accurate coverage of the target volume, significant normal breast tissue sparing was achieved. A prospective phase I trial is ongoing to evaluate this technique.

Future directions and recommendations

So far, four general strategies have been investigated in reducing interobserver discrepancies among radiation oncologists. These approaches help to improve the consistency of tumor bed delineation, but each has its own limitations. A delineation guideline is designed to be implemented by individual clinicians with their own interpretation and judgment and therefore, the results can be subjective. Surgical clips are often regarded as a clinical standard, but there are questions over their accuracy in defining the lumpectomy cavity, as clips only define a few points around the cavity's border, which is highly deformable, and require subjective interpolation, resulting in delineation inaccuracies. Multimodal imaging only detects tumor bed surrogates, such as the original tumor in pre-operative CT, electromagnetic features of the tumor bed in MRI, seroma in the lumpectomy cavity in US, and inflammatory tissue around the excision site in PET. These surrogates may not necessarily represent the true tumor bed, and as a consequence, the size of the TBV delineated from these images varies with the imaging modalities [51,55,56,62,63].

The current standard in multiple ongoing trials use the combination of standardized guidelines and surgical clips or fiducial markers to improve an observer's ability in delineation and observers consistency [34]. At Memorial Sloan-Kettering Cancer Center, we also adopt this strategy in tumor bed delineation for APBI. However, these strategies do not necessarily address the accuracy in tumor bed definition. While some studies have correlated pathology to multimodal imaging [63–65] and others have addressed inter-/intra-fractional TBV variations [23,66–68], these studies mostly focus on tumor bed margins required for EB APBI and have been conducted with small patient series.

We see a need for a systemic, multidisciplinary investigation involving radiology, surgery, pathology, radiation oncology, and medical physics. First, it is important to find out what is the most appropriate pre-operative imaging modality in defining the tumor extended by pathologic correlation. A direct comparison of pre-operative imaging to tumor involvement in the lumpectomy specimen is required. Second, as we know surgical techniques can heavily influence the shape and size of the lumpectomy cavity, studies are required to better define the benefit in the standardization of surgical clip placement. Furthermore, as clips can be displaced with the expansion and contraction of the surgical bed, studies correlating intraoperative imaging and serial post-operative imaging may be valuable to better understand clip displacement before treatment planning. Lastly, we see a need for further investigations in deformable image registration to aid physicians in better defining the most appropriate treatment volume. It is currently a challenge to reliably utilize deformable image registration techniques to register images of two different imaging modalities, such as CT and MRI [68–70], possibly due to the lack of internal landmarks in breast imaging to serve as anchor points for deformable registration. Additional work is required to produce dependable

results with deformable image registration for physicians to compare pre-operative tumor volume with post-operative TBV and treatment planning volume.

Concluding remarks

As APBI continues to gain popularity, accurate definition of the lumpectomy cavity is crucial. EB APBI is being investigated in multiple ongoing studies. As interobserver variability is indicative of observers' abilities to accurately define the treatment target volumes, variation in tumor bed delineation can potentially influence the results of the ongoing trials. Nevertheless, we recognize this is also representative of the current clinical practice environment. Using surgical clips placed in the lumpectomy cavity at the time of BCS to guide tumor bed delineation on CT is the method of choice in ongoing APBI studies [22–24] (Table 4 summarizes these ongoing trials). Although a similar CTV margin is being used in the ongoing trials (1.5 cm), the expansion of CTV to PTV varies (0.5–1.5 cm) [65].

In addition to improving tumor bed delineation accuracy and reproducibility, the optimal margin required for CTV and PTV for EB APBI continues to be an area of active investigation. As stated above, tumor is often eccentric in a lumpectomy specimen. Studies correlating tumor bed and the original tumor location may help clinicians better understand whether a concentric expansion of the lumpectomy cavity is suitable in defining the clinical target volume, and studies of various 2D and 3D image guidance techniques for EB APBI delivery may provide further insight on the appropriate margin needed for PTV to account for daily setup variations.

In summary, investigators have tested multiple methods in reducing observer variability and improving delineation accuracy when contouring the lumpectomy cavity for EB APBI. Using standardized guidelines coupled with CT/surgical clips remains the current gold standard in limiting observers' variability. Nonetheless, this approach may be insufficient in specific patients, such as those with a closed cavity [41]. In patients without closed cavity and with seroma formation, the seroma could also induce errors, as it may not represent the primary tumor bed but rather the surgical excision cavity. Further investigations are needed to explore approaches for specific patient populations, and the integration of MRI or US in addition to CT/surgical clips may be beneficial for those with dense breast parenchyma or poorly visualized cavities.

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