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The place of the boost in the Breast Cancer Treatment: State of Art

Short title: CTV_boost in breast cancer

Arnaud Beddok^{1,2} MD, Youlia Kirova¹ MD, Fatima Laki³ MD, Fabien Reyat³ MD PhD, Anne Vincent Salomon⁴ MD PhD, Vincent Servois⁵ MD, Alain Fourquet¹ MD

1. Department of Radiation Oncology. Institut Curie. Paris/Saint-Cloud/Orsay. France
2. Laboratory of Translational Imaging in Oncology (LITO). UMR (U1288). Institut Curie. Orsay. France.
3. Department of Surgery. Institut Curie. Paris. France
4. Department of Pathology. Institut Curie. Paris. France
5. Department of Radiology. Institut Curie. Paris. France

Corresponding author: Arnaud Beddok, Department of Radiation Oncology, 25 rue d'Ulm 75005 Paris; +33144324504; arnaud.beddok@curie.fr; a.beddok@gmail.com

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Abstract

Several randomized controlled trials have demonstrated the benefit of a boost to the tumor bed (TB) to reduce the risk of ipsilateral breast tumor recurrence. Recent technological progress has facilitated improved conformation of isodoses around the target volume. The accuracy and reproducibility of TB delineation have become even more essential. The purpose of this study is to review the extant knowledge on the boost delineation in breast cancer, focusing on interobserver variability (IOV) and the influence of various factors, such as the presence of clips or different imaging modalities to improve IOV. Most studies investigating IOV for boost delineation have shown poor reproducibility (with comparison indices such as the dice similarity index around 0.5). Clips in the lumpectomy cavity (LC), postoperative fluid accumulation in the LC and/or high cavity visualization score appeared to be associated with improved IOV. Likewise, the use of preoperative imaging (CT and/or MRI) may also be useful in improving the accuracy of TB definition but without any real gain in terms of IOV. Moreover, the delineation of boost has become even more challenging since the development of oncoplastic surgery. To improve the reproducibility and the accuracy of boost delineation, this review suggests that within each center, a group of multidisciplinary experts, including surgeons, radiation oncologists, pathologists, and radiologists, should convene to develop local guidelines, which may include the choice of preoperative imaging, the number and location of surgical clips, pathological margins, and orientation. The elaboration of contouring atlas is certainly of great assistance.

Keywords: target delineation, interobserver variability, interdisciplinary communication

1. Introduction

In 2020, female breast cancer (BC) has become the most commonly diagnosed cancer (with an estimated 2.3 million new cases, representing 11.7% of all cancer cases) and the fifth leading cause of cancer mortality worldwide, with 685,000 deaths [1]. In 2011, the ECBCTG meta-analysis showed that radiation therapy (RT) after breast-conserving surgery (BCS) decreased the risk of local recurrence (LR) from 25% without RT vs. 8% with RT, and reduced BC mortality by about one-sixth [2]. However, since the introduction of this procedure, it remained unclear which radiation dose is needed for patients treated by lumpectomy for early BC. The EORTC therefore decided to conduct a randomized controlled trial to investigate the potential advantage of delivering a higher radiation dose to the tumour bed (TB) after whole-breast irradiation at a dose of 50 Gy over 5 weeks [3]. The final analysis with a follow-up of 20 years suggested that the risk of ipsilateral breast tumour recurrence (IBTR) was reduced in patients who received a boost dose of 16 Gy from 16.4% to 12% without RT and with RT, respectively [4]. However, in this study, the authors did not specify how they delineated the boost volume. Moreover, a quality assurance study of this EORTC 'boost vs. no boost' trial showed that the absence of boost delineation constituted one of the main protocol deviations [5], as target volume delineation was missing on the treatment plans in as many as 67% of cases. Multivariate analysis of the prognostic factors for local control also failed to include boost delineation and technique [6]. Several RCTs have demonstrated that intensity-modulated RT (IMRT) for BC decreases acute and late toxicity [7,8]. Accelerated partial breast irradiation after BCS can also be an option for selected patients [9]. The accuracy of boost target volume delineation appears to be particularly important in this setting. The goal purpose of the present study was to review the essential knowledge on boost delineation in BC, focusing on intra- and interobserver variability (IOV) and the influence of various factors such as the presence of clips or different imaging modalities to improve IOV.

2. Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "boost AND breast AND delineation", "boost AND breast AND segmentation", "lumpectomy cavity AND delineation", "interobserver variability AND boost AND breast cancer", "boost AND breast cancer AND imaging" from 1990 until June, 2021. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

3. Oncoplastic breast-conserving surgery

The success of BCS for the treatment of BC is based on the principle of complete excision of the cancer by ensuring adequate surgical margins, while simultaneously preserving the natural shape of the breast. Oncoplastic surgery (OPS) emerged two decades ago as a new approach to allow wide excision for BCS without compromising the natural shape of the breast [10,11]. A wide range of techniques have subsequently been

proposed and can be selected according to the size and shape of the breast and the size and location of the tumour [12]. A consensus conference in 2017 reviewed the indications, classifications and techniques of OPS [13]. According to the Clough system, OPS procedures are currently classified into two levels: level I when < 20% of the breast volume is excised and level II when 20-50% of the breast volume is excised. This classification also includes a quadrant-by-quadrant atlas to suggest one or more specific techniques depending on the exact location of the breast tumour, which have been described in detail elsewhere [14]. In level I, for glandular resection, full-thickness excision is performed from the subcutaneous fat underlying the skin to the pectoralis fascia. Before closing the defect, metal clips are usually placed on the lateral edges of the resection bed to help surgical bed definition at the time of RT. During standard BCS, breast tissue is either reapproximated or left open, allowing the possible formation of a hematoma or seroma. In the case of large lesions, requiring extensive resections, breast tissue can be mobilized from the lateral areas of the remaining gland or recruited from the central part of the breast. The TB is in this case relatively distant from its original position. This is especially true for level II OPS, in which at least 20% of breast tissue is removed.

4. Pathological evidence supporting tumour bed boost following breast-conserving surgery

In 1985, Holland et al. analyzed 413 mastectomy specimens to provide an estimate of the amount and pattern of tumour foci that may remain in the breast after BCS [15] and selected the 315 of these 413 patients who would probably have been considered eligible for BCS for this analysis. The distance between the primary tumour border and each of the other tumour foci was measured for each case. Regardless of the size of the initial tumour, most of the residual disease (57%) was located within 2 cm of the initial tumour. Moreover, 42% of patients with T1 disease had tumour foci located more than 2 cm from the initial tumour and 10% had foci located more than 4 cm from the initial tumour. These observations were consistent with earlier results obtained by Rosen et al., who showed that 74% of tumour foci were located around the index tumour [16]. According to the pathological findings of the NSABP protocol B-06, 95% of IBTR were observed at or close to the same quadrant as the index cancers [17]. In 1995, Ohfake et al. studied the intraductal extension of invasive primary BC in 20 patients treated by BCS. The average maximum distance of intraductal extension was 11.9 mm. In a more recent study, Vicini et al. (2004), using computer graphic three-dimensional reconstruction, analysed breast resection samples from 333 patients who underwent resection prior to RT to measure the greatest extent of any residual disease (ductal carcinoma in situ [DCIS] or invasive cancer) around the initial lumpectomy cavity (LC) [18]. The extension distance from the edge of the initial excision site was 0 mm, between 0 and 5 mm, 5 and 10 mm, 10 and 15 mm, more than 15 mm in 35.7%, 20.1%, 24.9%, 10.2% and 9% of cases, respectively. The authors concluded that a 10 mm margin around the TB should be sufficient to cover any disease remaining in the breast after lumpectomy in >90% of patients.

These various studies suggested that a margin of 1.5 to 2 cm around the tumour or TB should be sufficient to eradicate most intraductal and invasive microscopic extension. Nevertheless, in a large meta-analysis assessing optimal margins, analysis of the relationship between specific margin widths (1 - 5 mm) and IBTR failed to

identify any association with margin distance or any statistical evidence for a trend suggesting a decreased rate of IBTR with increased negative margin widths [19]. Experts therefore recommended the use of no ink on tumour as the standard for adequate margins.

5. Clinical evidence supporting tumour bed boost following breast-conserving surgery

Table 1 summarizes the results of nine selected clinical studies supporting the value of TB boost after BCS [4,20–27]. Despite different follow-ups, these studies show that, regardless of treatment (BCS alone, BCS followed by RT without boost, or BCS followed by RT with boost), IBTR mainly occurred at the same site as the original tumour (44 - 80% of cases). In particular, two major clinical studies demonstrated improved locoregional control rates when patients received a boost to the TB. In 1997, Romestaing et al. prospectively compared the outcome of 1,024 patients with BC treated by local excision and randomly assigned to receive either no further treatment (49%) or a 10 Gy electron boost to the TB (51%) [25]. With a follow-up of 5 years, the IBTR rate was lower in the boost group (3.6 % vs. 4.5%). Moreover, cosmetic results, with 10-15% of fair cosmesis, were not significantly different between the two groups. The international “boost vs. no boost” clinical trial compared outcomes and toxicities of 5,318 patients with early BC treated by BCS and whole breast irradiation followed by either no further local treatment (50%) or an additional localized dose of 16 Gy [28,29]. With a median follow-up of 17.2 years, LR was more frequent in the no boost group: 13% vs. 9% ($p < 0.001$). Forty-four percent of LRs occurred in the primary TB, 8% in the scar, 11% were diffuse in the breast, 28% were located outside the original tumour area, and the location was not specified for 9% [4]. Young age (< 40 years), presence of DCIS, and high-grade tumour were significantly associated with a higher risk of local relapse, and would require TB boost [6].

Interestingly, none of these studies specified how the authors delineated the boost volume. However, as described below, there can be marked intra- and IOV concerning boost delineation, which can have an impact on interpretation of the results.

6. Intra- and interobserver variability of breast tumour bed delineation

6.1. Definitions

As in other organs, the methodology and indices used in these IOV studies are often different [30]. Different words are commonly used to describe the location of the tumour prior to resection: “tumour bed”, “lumpectomy cavity”, “seroma cavity” are usually synonymous. Several scores are currently used to assess visualization of the TB. The Seroma Cavity Score (SCS) is a system developed by Kader et al. in 2004 to grade the clarity and ease of delineation of the seroma according to a 6-point scale, ranging from “0=no seroma” to “5=clearest” [31]. The Cavity Visualization Score (CVS) was subsequently described to grade visualization of the LC, ranging from “1=cavity not visualized” to “5=all cavity margins clearly visualized” [32]. Several indices are also used for analysis of intra- and IOV [33]. The contours established by different observers are generally compared

to an expert contour. The Conformity Index (CI) corresponds to the sum of the intersections of all possible volume pairs divided by the sum of their unions [34].

6.2. Assessment of intra- and interobserver variability for breast tumour bed delineation

IOV studies of TB delineation based on the above methods and indices have reported a high level of intra- and IOV, regardless of the RT technique used to deliver the boost [35–45] (Table 2). For instance, in 2005, Struikmans et al. evaluated IOV of CTV delineation of glandular breast tissue and the boost [36]. The mean CI for the CTV_boost was 0.56. The presence of clips in the LC, the position of the lumpectomy scar on the skin, postoperative fluid accumulation in the LC, and the location of the tumour on preoperative ultrasound and mammography were helpful for delineation of the CTV_boost. In 2007, Petersen et al. examined IOV of the target volume for partial breast radiotherapy planning and evaluated the characteristics associated with low interobserver concordances [35]. Features associated with reduced concordance included tissue stranding from the surgical cavity, proximity to the muscle, dense breast parenchyma, and benign calcifications that may be mistaken for surgical clips. Major et al. investigated IOV of target volume delineation in accelerated partial breast irradiation with multicatheter brachytherapy [40] and observed significant IOV of LC and PTV delineation among participants. In the first phase, all investigators performed delineations according to their experience and best knowledge. In phase 2, investigators had to comply with the following guidelines: seroma contouring only comprised the visible seroma with homogeneous background, surgical changes such as breast tissue protrusions around the excision cavity had to be excluded, and clips had to be surrounded by the contour with close contact. IOV decreased between these 2 phases.

6.3. Importance of surgical clips to determine the position of the tumour bed

Surgically placed clips or postoperative seroma are commonly used to determine target volume [43,46–48]. In 2003, Benda et al. compared two techniques to determine the position of the TB [46]: a clinical technique in which the position of the TB was determined by palpation and the position of the scar and another technique in which the TB was located by using clip locations. The second technique provided better results. In 2010, Kirova et al. demonstrated that the use of three or more clips during lumpectomy improved the accuracy of TB delineation [47]. In 2010, Shaikh et al. showed that the presence of gold fiducial markers placed at the time of surgery could improve interobserver delineation of the TB and CTV_boost [43]. In 2015, Lewis et al. also showed that the absence of surgical clips could be critical for tumour localization [48]. Finally, in Atrchian's study, the presence of clips significantly increased the average LC volume [49]. The presence of clips has also improved the consistency of delineation by significantly decreasing the standard deviation [50]. Cross et al. also recently proposed a novel 3-dimensional bioabsorbable marker, which was used during breast-conserving surgery in 108 patients and showed that the use of this marker was a safe and effective method for delineating the TB [51]. The presence of clips is even more important in the case of OPS. In 2014, Furet et al. showed in a cohort of 31 patients, including 18 who had OPS, that the presence of at least 3 clips was necessary to define the tumor bed and improve interobserver reproducibility in the case of OPS (this point is discussed below) [52].

Finally, mean CI, overlap index or Dice similarity coefficient were equal to about 0.5. Clips in the LC, postoperative fluid accumulation in the LC and/or high CVS appeared to be associated with improvement of this IOV. The following section proposes several imaging solutions designed to improve TB delineation in order to improve IOV.

7. Imaging for breast tumour bed detection

7.1. Preoperative imaging

7.1.1. Preoperative CT

Several authors have studied the influence of preoperative CT on IOV and CTV_boost volumes [53–57] (Table 3). The results of these studies are controversial: some authors showed that preoperative CT could be useful to decrease IOV [53–55], whereas others showed that preoperative CT was associated with higher IOV [56]. In 2008, Kirova et al. proposed an 8-step method to improve IOV using preoperative CT. Gonzalez et al. evaluated the difference between the GTV delineated on preoperative CT and TB delineation based on clip position [57]. The maximum margin necessary to include all of the TB was 4.5 cm. Lesions located in the upper outer quadrant required the widest margins.

7.1.2. Preoperative MRI

In 2017, Zhang et al. performed a comparative study of gross tumour volumes determined by preoperative MRI, postoperative specimens and TB [58]. Thirty-three patients with BC who underwent preoperative MRI and radiotherapy after BC surgery were enrolled. The GTV of the TB delineated on planning CT was significantly larger than the GTV observed on MRI and the real GTV on pathology, whereas no significant differences were observed between the GTV delineated on MRI and the real GTV on pathology.

7.2. Postoperative imaging

Several studies have assessed the value of MRI in the supine or another position to improve TB delineation [59–62,32]. In a study published in 2009, based on 30 women in whom 6-12 titanium clips were secured in the excision cavity walls at lumpectomy, Kirby et al. [59] compared the TB delineated on planning CT scans and on MRI performed just after the CT scan. The TB was delineated on CT by a single observer without reference to MR findings, using clips, seroma, and architectural distortion. The TB was also outlined on the MR at least two weeks after CT outlining by the same observer blinded to CT findings, with the T2W sequence and encompassing any visible seroma, fibrosis, and clips. Addition of MRI to CT increased the TB volume by identifying additional seroma, oedema and hemorrhage [59]. MRI could potentially be very useful when clip placement inside the TB is not performed during BC surgery. In 2011, Jolicoeur et al. performed a prospective study to assess the IOV of surgical bed (SB) delineation on CT and supine MR [60] in 70 patients who had undergone breast-conserving surgery without clips in the SB and scheduled to undergo brachytherapy as part of their adjuvant breast RT.

Three radiation oncologists had to delineate the SB on MRI and CT imaging, without access to the surgical report, pathology report or mammogram. For MRI, the SB was delineated on the T2-weighted images and was defined as a change in anatomy compared to the normal contralateral side, a mass effect, nodular or infiltrative abnormal tissue, fat replacement, and decreased signal intensity. For each observer, volumes obtained on MR images were smaller than those based on CT images. A highly significant IOV for delineation of the SB on CT was demonstrated, whereas all three observers agreed on the volume of the SB delineated on MR. In a similar study performed in 2017, the authors quantified IOV and accuracy for CT- and MRI-based segmentation of the LC CTV (CTV_{LC}) in 12 patients without clips [32]. Five radiation oncologists delineated CTV_{LC} on both modalities and had to comply with the following instructions: they had to use the T2-weighted FSE images as primary data set, delineate the LC as post-lumpectomy intramammary changes, compare findings with contralateral anatomy to identify differences in geometry, tissue architecture, formation of seroma, hepatoma and scar tissue, fat replacement on CT and decreased signal intensity on MRI. Mean CTV_{LC} were similar. However, mean conformity index (CI) was superior for MRI and the authors concluded that MRI improved visualization of post-LC changes, reduced interobserver variation and improved the accuracy of CTV_{LC} contouring in patients without clips in TB. In 2012, Giezen et al. evaluated the IOV of LC delineation based on either CT or MRI in the treatment position [61]. MRI did not provide any additional information compared to CT in cases with a low CVS. The conformity index (CI) was lower for MRI than for CT, especially in cases with a low CVS due to greater centre of mass (COM) shifts for MRI, probably caused by adequate visibility of the surgical clips on MRI. Furthermore, Mast et al. (2014) evaluated whether delineations based on co-registered CT and MRI may result in an improved consistency between observers for delineating the LC of 15 patients with both CT and MRI in supine position [62]. The authors compared mean IOV (by calculating conformity index) between CT-based and MRI-based LC delineation and did not find any significant difference. They also calculated the cavity visualization score and showed that, for patients with $CVS > 4$, the mean CIs of the LC were higher compared to $CVS < 4$ for volumes delineated on both CT and CT/MR images.

7.3. Other imaging modalities

In 2008, a study involving 12 patients with BC evaluated the use of PET to improve LC delineation and treatment planning [63]. Increased FDG uptake was likely a result of postoperative inflammation in the LC. The targets defined using PET/CT were significantly larger than those defined with CT alone. Chiu et al. have also recently developed a volumetric Ultrasound Tomography image guidance system for stereotactic partial breast irradiation in the prone position [64].

On the basis of these studies, CI and CTV_{boost} (or TB, LC) volumes did not appear to be improved by using preoperative CT, or preoperative or postoperative MRI. Nevertheless, the methods of Kirova and Boersma [53,54] allowed to significantly reduce the volume of TB, and thus to reduce the risk of radiation-induced fibrosis.

8. Uncertainties and CTV/PTV margin around the tumour bed

8.1. CTV margins

The margin from TB to CTV_boost is generally isotropic or anisotropic. For isotropic margin expansion, a symmetric margin (same margin in all directions) minus the minimal tumour-free margin, as described in the pathology report, is added to the TB. Historically, this margin should be 15 mm [15]. The idea of anisotropic margin expansion, taking into account the 3D pathological margins, was also introduced to reduce the boost volume without compromising target coverage [65]. Kirby et al. (2013) studied the impact of the number of clips on the CTV_boost margin to be used around the tumor bed [66]. They concluded that, when target definition was based on 0 or 1 implanted markers, large additional margins were required to account for uncertainty concerning the true TB location. Five implanted markers were therefore likely to be adequate, assuming the addition of a standard 10-15mm TB-CTV margin. Verhoeven et al. (2016) also demonstrated that the use of anisotropic margin expansion significantly reduced the volume of the delineated CTV_boost (94cc vs. 50cc), but substantially increased the IOV (Jaccard index = 0.73 vs. 0.51) [67].

8.2. Positional uncertainties – PTV margins

There are several types of errors that require the use of a PTV margin around the CTV_boost in BC. Harris et al. (2012) [68] showed that PTV margin contributions from deformation errors were small in comparison to other sources of error, such as set-up and delineation. The position of the TB kept changing during the course of treatment, as the treatment position was aligned to bony anatomy. Lee et al. (2012) analyzed the positional uncertainties between bony anatomy and TB [69]. In their study, the TB, called CTV-H, was defined by incorporating the anatomy of seroma, adjacent surgical clips, and any architectural distortion on CT simulation. In their analysis, a larger breast thickness, larger breast volume, higher BMI and different tumour locations correlated with greater positional uncertainty of the TB. These uncertainties should be taken into account in order to improve treatment efficacy and toxicity. Chen et al. (2014) [70] also showed that the LC volume could significantly change between the planning CT and the start of irradiation. Adaptive repositioning plans allowed improvement of target coverage. Significant changes in lumpectomy site, shape, and volume at the time of the boost that deviated from the original plan for whole breast irradiation with sequential boost were observed, suggesting that adaptive replanning could be useful.

9. Critical discussion

This review showed that there is sufficient preclinical and clinical evidence in the literature to conclude that a boost dose to the breast TB allows increased local disease control, in particular for young people (< 40 years), and high-grade tumour [6]. However, the literature also revealed a marked IOV in terms of TB/SB/CTV_boost delineation, and several ways to improve this IOV have been proposed (clips in the SB, visible LC, preoperative CT).

This review confirmed that, regardless of treatment (BCS alone, BCS followed by RT without boost, or BCS followed by RT with boost), IBTRs predominantly occur in the same site as the initial tumour (Table 1). Three hypotheses can be proposed to explain this observation. The first hypothesis is that the presence of radioresistant tumour cells (e.g., cancer stem cells) at the initial tumour site would require higher doses of irradiation to be sterilized. The final results of the "Young-boost" trial (NCT00212121), which compares TB irradiation at a dose of 16 Gy vs. 26 Gy for young women, should certainly provide an answer to this question. This trial has already shown that photon boost, high boost dose, poor cosmesis before radiation therapy, large boost volume and adjuvant chemotherapy were predictors of poor cosmetic results [71]. The second hypothesis is that IBTR does not constitute a true recurrence, but a second cancer, possible radiation-induced [23]. Nevertheless, as demonstrated by at least two studies [27,72], LRs are mostly true genomic recurrences. Finally, IBTRs at the initial tumour site could be due to incorrect localization of the TB. As indicated above, none of the studies that validated the indication for boost radiation therapy specified how the boost dose target was delineated. One approach to assess the role of incorrect tumour localization would be to study the results of patients in whom the boost dose is delivered by using different techniques (Table 1), as, for the same prescribed dose, irradiation of the TB can be very different depending on the technique used (Figure 1). Typically, in the EORTC "boost vs. no boost" trial, several different techniques were used for boost irradiation, at the discretion of the physician: electrons, wedge-shaped oblique photon beams, or brachytherapy (with a ^{192}Ir implant). [4]. However, the outcomes of these three groups were not compared. Note that, in their study comparing the efficacy and toxicities in 701 early BC patients receiving a boost to the tumour excision site with either electron beam (64%) or interstitial ^{192}Ir implants (36%), Perez et al. did not find any difference between electron and brachytherapy, particularly in terms of cosmetic results with almost 20% of fair or poor cosmesis in both groups [73].

This review also highlights the very high intra- and IOV associated with boost delineation. The presence of surgical clips, postoperative fluid accumulation in the lumpectomy cavity, and clear visualization of the cavity would allow improvement of this IOV. The surgical procedure therefore has a very high impact on the magnitude of IOV. Moreover, as discussed in the first section, in the case of large OPS, surgical clips may be located quite distant from the initial tumour location, as confirmed by trials using preoperative CT to assist in TB delineation [74]. Preoperative imaging therefore cannot always be used to delineate the TB, and only the position of the clips and postoperative remodeling can provide an indication of this location. TB delineation by the radiation oncologist is therefore a very complicated procedure, which depends on the presence of serum, clips, and especially tissue displacement in case of OPS (Figure 2).

Ultimately, as clearly illustrated by a large number of studies, the radiation oncologist's experience must always prevail over other factors. Ideally, the radiation oncologist should be present right from the beginning of the patient's care, to perform clinical examination before the procedure and to analyze the mammogram together with the expert radiologist. The radiation oncologist should also be present with the surgeon in the operating

room and with the pathologist during pathological examination of the surgical specimen. However, such an ideal approach is clearly impossible, given the large number of patients requiring postoperative RT for BC.

Two methods could nevertheless improve CTV_boost delineation and the associated IOV. First, in each centre, a cohort of experts should convene to develop local guidelines, as conducted at the Institut Curie by Kirova et al. [53]. Such guidelines could include the choice of preoperative imaging (especially CT or MRI), the number and location of surgical clips, and pathological margins and orientation. Second, the elaboration of contouring atlas is surely also of great help. The contouring atlases resulting from interobserver studies are particularly noteworthy [54]. For instance, Boersma et al. proposed in 2012 a contouring atlas (in supp. data of the original article [54]) with figures that allow to take into account the existence or not of a lymphocele, and the size of the surgical resection margin. Second, the elaboration of contouring atlas of such as that of the GEC ESTRO is surely also of great help. Moreover, in 2016, GEC ESTRO BC Working proposed guidelines for target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery [75,76]. The cavity visualization scoring (CVS) had to be at least 3 in order to minimize the IOV. At delineation of surgical cavity, only the homogeneous part of the post-operative seroma has to be included in the contours and protrusions or sharp irregularities have to be excluded. When surgical clips are present, they have to be surrounded by the contour with close contract. CTV was created from the outlined surgical cavity with an anisotropic geometrical expansion. In each direction, the safety margin is calculated by taking onto account the size of the free resection margin. The total size of safety margin is always 20 mm which is the sum of surgical and added safety margins.

10. Conclusion

Determination of the IOV of TB delineation is essential to improve the quality of the treatment for our patients with BC. This accuracy should also allow improving the quality of clinical trials comparing boost vs. no boost in BC. Surgical clips should always be placed in the surgical bed to improve TB delineation. Preoperative CT does not appear to be necessary to improve TB delineation, particularly when OPS has been performed. However, postoperative MRI could be useful, in compliance with TB delineation guidelines, in particular in the absence of clips. CTV and PTV margins must also be determined at a multidisciplinary meeting, taking into account surgical margins (for CTV) and intrafractional TB motion (for PTV). Other studies should be performed to establish new delineation guidelines, based on multidisciplinary (surgeon, pathologist, radiologist, and radiation oncologist) observations, to improve the accuracy of the delineated TB and the IOV of delineation.

11. Conflict of interest statement

None to declare.

12. References

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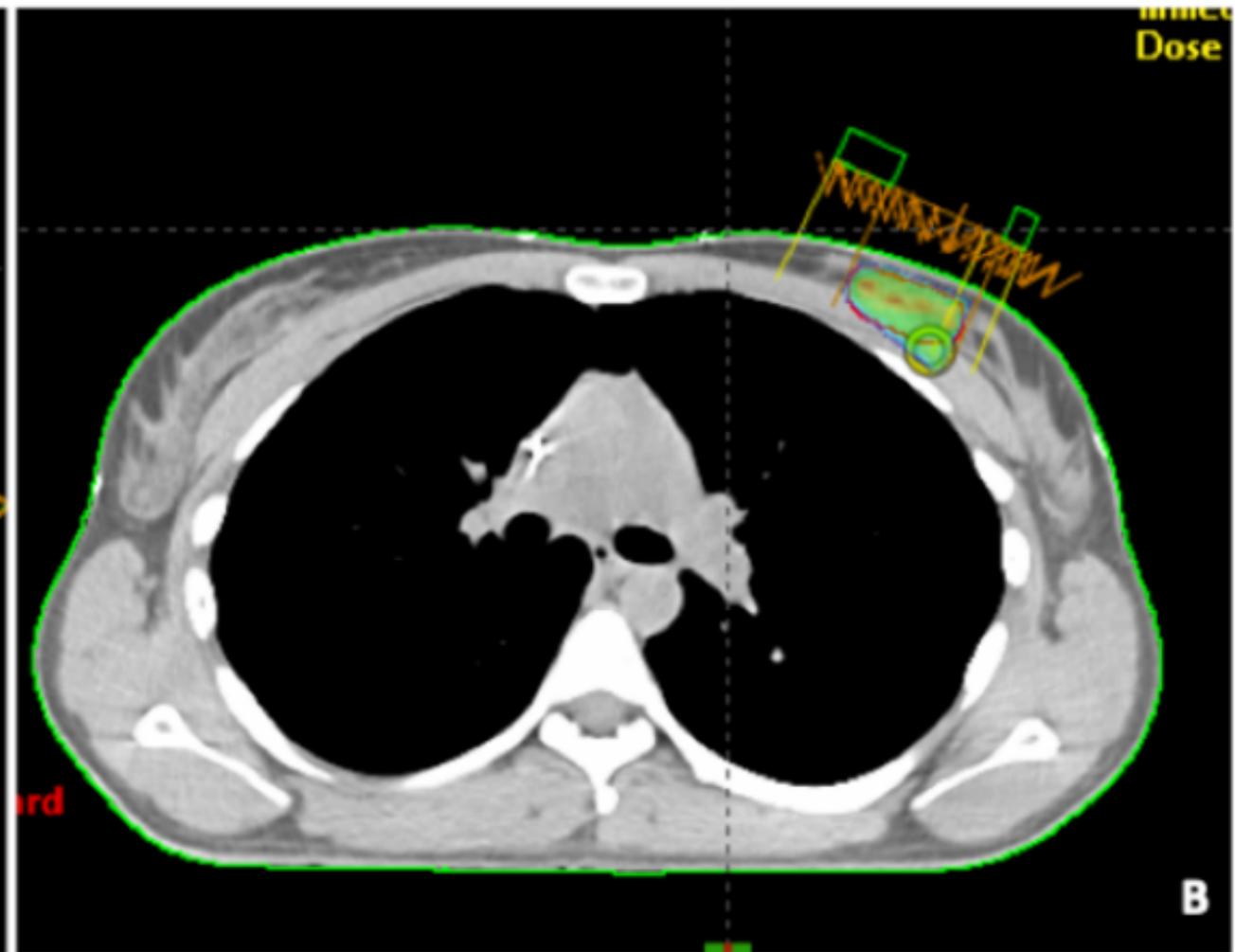
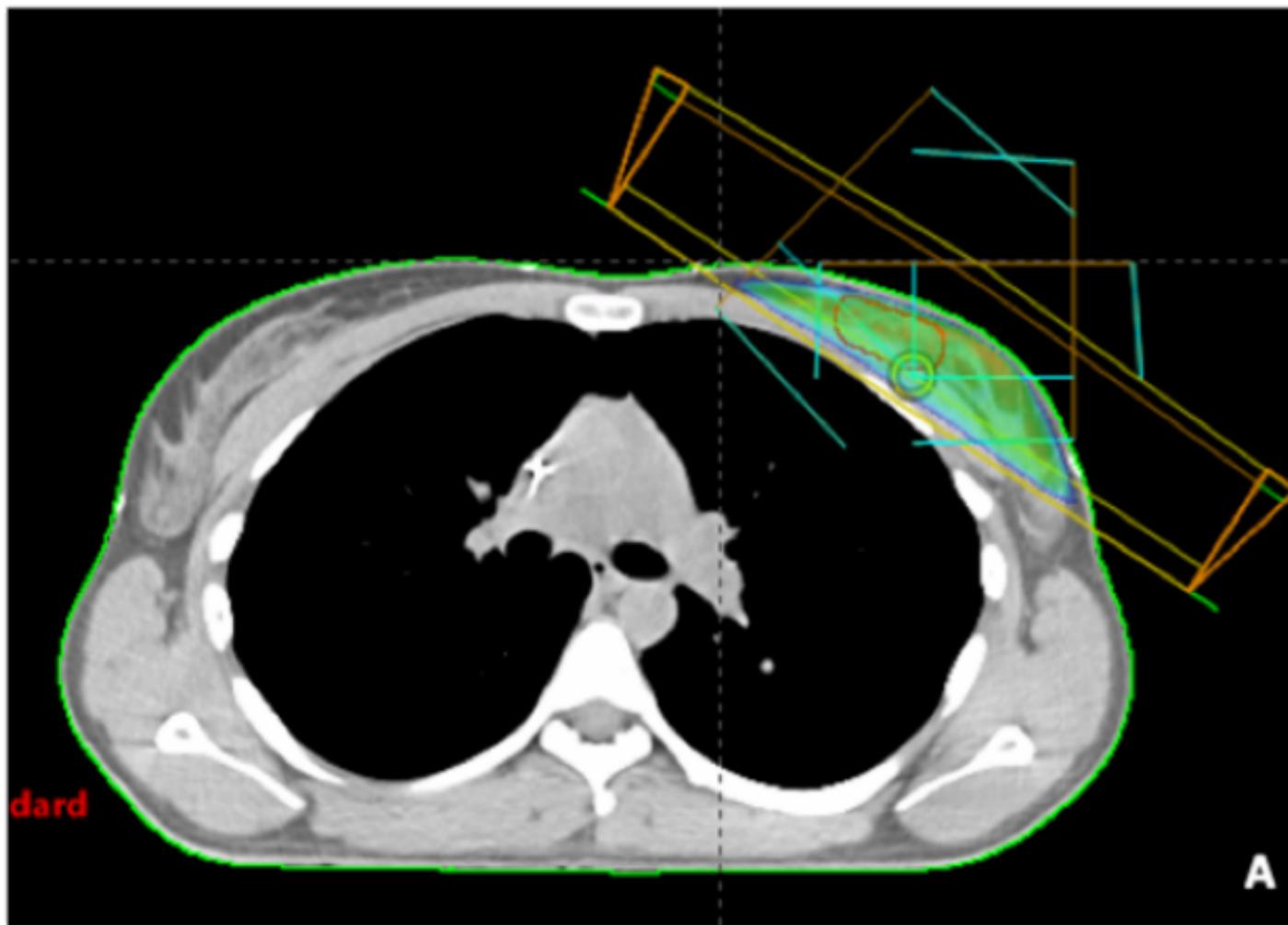
13. Figures Legends

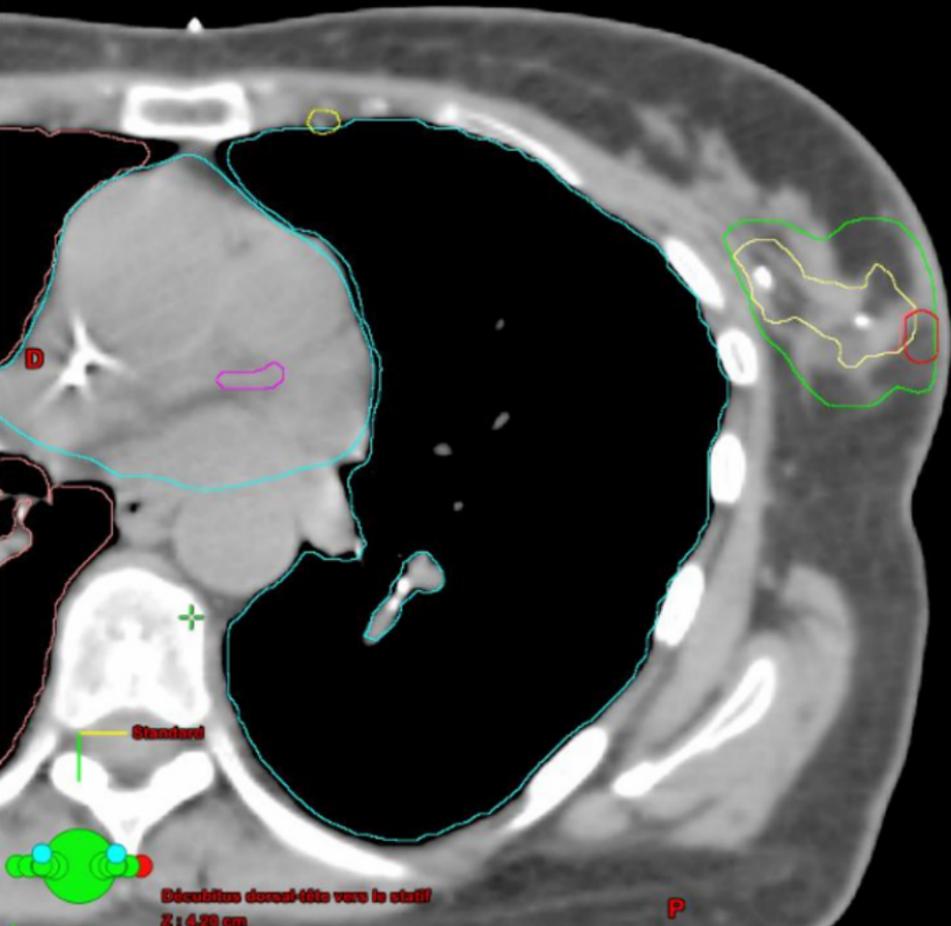
Figure 1: Dosimetric comparison 3D-RT vs IMRT for boost BC irradiation

Abbreviations: 3D-RT: three-dimensional radiation therapy, IMRT: intensity-modulation radiation therapy. 1A: irradiation of the CTV_boost (red line) with two tangential opposing megavoltage photon beams, 1B: irradiation on the CTV_boost (red line) with one direct anterior megavoltage photon beam with IMRT. For the same delineated CTV_boost, isodose distribution (color wash) would be very different between both irradiation techniques.

Figure 2: CTV_boost definition after oncoplastic surgery

This figure illustrates the difficulty of CTV_boost definition after OPS. In this example, the dosimetric CT was merged with a preoperative CT. The red line represents the TB defined on preoperative CT. The yellow line represents the surgical bed defined on dosimetric CT on the base of clips position. The green line is the CTV_boost which includes both tumour and surgical beds.





G

CT-26/08/10



CT_pre op

Stabilité dorsale-tête vers le staff
Z : 4.28 cm

Table 1: Clinical evidence for tumor bed boost following conservative breast surgery

	Number of patients		Radiotherapy		Technique		Follow-up (years)	Number of IBTR		Number of IBTR in the site of the initial surgery
	RT	no RT	WBI	Boost	WBI	Boost		RT (boost vs no boost)	no RT	
Clark 1992 [20]	416	421	416	416	EBTR (⁶⁰ Co)	EBTR (⁶⁰ Co)	3.6	23	108	112 (80%)
Liljegren 1999 [21]	184	197	184	0	EBTR (4 – 10 MV LINAC or ⁶⁰ Co)	na	10	13	44	38 (67%)
Touboul 1999 [22]	528	0	528	528	EBTR (4 – 6 MV LINAC or ⁶⁰ Co)	EBTR (4 – 6 MV LINAC or ⁶⁰ Co)	7	44		32 (76%)
Smith 2000 [23]	1152	0	1152	1152	EBTR	EBTR (electrons)	14.2	136		136
Veronesi 2001 [24]	294	273	294	294	EBTR (6 MV LINAC or ⁶⁰ Co)	EBTR (ortho voltage)	9	16	59	59 (78.6%)
Romestaing 1997 [25]	1024	0	1024	521	EBTR (4 – 10 MV LINAC)	EBTR (9 - 12 MeV electron)	3.3	30 (10 vs. 20)	na	na
Polgar 2002 [26]	207	0	207	104	EBTR (6 – 9 MV LINAC or ⁶⁰ Co)	EBTR (6 - 16 MeV electron) or HDR BT	5.3	23 (7 vs. 16)	na	16 (69%)
Galper 2005 [27]	2102	0	2102	2102	EBTR	EBTR	6	398	na	212 (53%)
Bartelink 2014 [4]	5318	0	5318	2657	EBTR (MV LINAC or ⁶⁰ Co)	EBTR (MeV electron) or HDR BT	17.2	591 (237 vs. 354)	na	261 (44%)

EBTR : External beam radiation therapy, HDR-BT : High-Dose-Rate Brachytherapy

Table 2: Analysis of intra and inter-observer variability of surgical bed delineation

Abbreviations: RT: radiation therapy, TB: tumour bed, IOV: intra and inter-observer variability, EBRT: external-beam radiation therapy, CI: conformity index, LC: lumpectomy

	RT technique for boost irradiation	Number of patients	Number of observers	IOV	Help for breast tumour bed delineation
Struikmans 2005 [36]	EBRT	18	5	Mean CI = 0.56	- clips in the LC - position of the lumpectomy scar on the skin - post-operative accumulation of fluid in the LC - pre-operative mammography/ultrasound pictures
Peterson 2007 [35]	EB-PBI	30	3	Mean CI = 0.61	- heavy mammary parenchyma - absence of benign calcifications (confusing with surgical clips)
Landis 2007 [37]	EB-PBI	34	4	Mean OI = 0.63	- post-operative accumulation of fluid in the LC
Li 2009 [38]	EBRT	3	9	Mean OI = 0.1	- clips in the LC - post-operative accumulation of fluid in the LC
Dzhugashvili 2009 [44]	EB-PBI	50	3	Median CI = 0.55-0.65	- clips in the LC - experience with breast RT
Van Mourik 2010 [39]	EB - PBI	8	13	Mean CI = 0.6 (0.2 – 0.8)	- clips in the LC - post-operative accumulation of fluid in the LC
Major 2015 [40]	Brachytherapy	5	9	Mean CI = 0.5 (0.4 – 0.6)	- experience with breast brachytherapy - high CVS
Guo 2015 [41]	EB-PBI	20	5	na	- high CVS - number of surgical clips > 5
Wang 2016 [45]	EBRT	35	4	DCS = 0.7 – 0.8	- high CVS - number of surgical clips \geq 5
Upreti 2017 [42]	APBI - MIB	20	5	Mean CI: 0.5 – 0.6	- high CVS

cavity, EB-PBI: external-beam partial breast irradiation, OI: overlap index, CVS = cavity visualization score, DSC: dice similarity coefficient, APBI: accelerated partial breast irradiation, MIB: multi-catheter interstitial brachytherapy, na: not available

Table 3: Imaging and tumour bed delineation

Imaging technique	RT technique for TB irradiation	Number of patients	IOV without vs with imaging	Volumes of CTV_boost without vs with imaging
<u>Pre-operative CT</u>				
Boersma 2012 [54]	EBRT	30	CI = 0.36 (no differences)	42 cc to 36 cc ($p = 0.005$)
Den Hartogh 2014 [55]	EBRT	14	CI = 0.80 (with preop-CT)	59 cc (with preop-CT)
Verhoeven 2016 [56]	EBRT	22	Jl = 0.50 vs 0.53 ($p < 0.001$)	50 cc (no differences)
<u>Post-operative MRI</u>				
Kirby 2009 [59]	EB - PBI	30	CI = 0.87 (no differences)	81.9 cc vs. 93.1 cc
Jolicoeur 2011 [60]	Brachytherapy	70	MR improves IOV ($p < 0.0001$)	no differences
Al Hammadi 2017 [32]	APBI	12	CI = 154 vs 152 (NS)	no differences
Mast [62]	EBRT	15	CI = 0.52 vs 0.48 (NS)	no differences
<u>Pre-operative MRI</u>				
Giezen 2012 [61]	EBRT	15	CI = 0.52 vs. 0.32	no differences
Zhang 2017 [58]	EBRT	32	na	no differences

CI: conformity index, Jl: Jaccard index, EBRT: external-beam radiation therapy, EB-PBI: external-beam partial breast irradiation, APBI: accelerated partial breast irradiation