The Breast 72 (2023) 103584

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

The King is in the altogether: Radiation therapy after oncoplastic breast surgery

Orit Kaidar-Person [a,b,*], Birgitte Vrou Offersen [c], Trine Tramm [d], Peer Christiansen [e], Tine Engberg Damsgaard [f], Ashutosh Kothari [g], Philip Poortmans [h,i]

[a] Breast Radiation Unit, Oncology Institute, Sheba Tel Hashomer, Ramat Gan, Israel
[b] Tel Aviv University, Israel
[c] Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark
[d] Department of Pathology, Aarhus University Hospital, and Department of Clinical Medicine, Aarhus University, Denmark
[e] Department of Plastic and Breast Surgery, Aarhus University Hospital, Denmark
[f] Department of Plastic Surgery and Burns Treatment, Copenhagen University Hospital, Copenhagen, Denmark
[g] Department of Breast Surgery Guy's Hospital London, UK
[h] Department of Radiation Oncology, Iridium Netwerk, Antwerp, Belgium
[i] Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

ARTICLE INFO

Keywords:
Radiation
Breast cancer
Oncoplastic
Boost
Radiotherapy

ABSTRACT

Breast cancer is the most common malignancy, and the majority of the patients are diagnosed at an early disease stage. Breast conservation is the preferred locoregional approach, and oncoplastic breast conservation surgery is becoming more popular. This narrative review aims to discuss the challenges and uncertainties in target volume definition for postoperative radiation after these procedures, to improve radiation therapy decisions and encourage multidisciplinary.

1. Introduction

Postoperative radiation therapy (RT) is an integral part of breast conserving therapy (BCT). Overall, it is estimated that up to 80% of stage I-III breast cancer patients will undergo RT as part of their primary breast cancer therapy [1]. Surgical techniques for primary treatment of breast cancer have advanced over the past decades to improve maintaining aesthetic outcome and symmetry with the contralateral breast. Oncoplastic breast surgery was initially applied to correct deformities after breast conserving surgery (BCS) and RT [2]. Clough and colleagues were leaders in developing this approach, initially to correct deformities and later also as primary approach for BCS [2–4]. These procedures, known as oncoplastic breast conserving surgery (OBCS), may include volume displacement within the breast, oncoplastic breast reduction (therapeutic mammoplasty), or volume replacements procedures [5,6]. Therefore, if planned correctly, it will achieve the ultimate goal of breast cancer surgery, combining radical oncological resection, preserving the breast, and achieving symmetry, if needed with contralateral aesthetic surgery to optimise symmetry.

Parallel to that, RT for breast cancer has evolved mainly thanks to better definition and visualization of the target volumes by using CT-based planning rather than bony landmarks [7,8] and by the understanding that dosimetry, RT planning, and quality assurance matter a lot for reducing RT-related toxicity, including the impact on breast aesthetic outcomes [9–11].

Overall, the oncological safety and patient reported outcomes of OBCS were recently summarized in a comprehensive Cochrane systematic review [12], indicating that these procedures seem to be safe, but it is supported by low-level evidence.

Key points that should be further mentioned out of the summary of the Cochrane systematic review [12] is that overall, OBCS seem to have similar local control as BCS, with lower re-excisions rate after OBCS. Re-excision rate should not be considered as a surrogate to clear margins, as it might subjected to considerable bias, considering that the technical challenges to perform a re-excision after OPBS might be higher compared to BCS. Indeed, uncertainties in the orientation of the close-positive margins after OBCS due to tissue manipulation may discourage performing re-excisions. Compared to BCS, OBCS is found to be associated with more recall for biopsies [12], partly related to formation of oil cysts, calcifications and fat necrosis following OBCS and

* Corresponding author. Breast Cancer Radiation Therapy Unit, Sheba Medical Center, Ramat Gan, Israel.
E-mail addresses: orit.kaiderperson@sheba.health.gov.il (O. Kaidar-Person), philip.poortmans@telenet.be (P. Poortmans).

https://doi.org/10.1016/j.breast.2023.103584
Received 5 August 2023; Accepted 24 September 2023
Available online 25 September 2023

RT. In a large population study, the rate of re-excision following OBCS was significantly lower than in BCS (14,1% vs. 15,6%, odds ratio (OR) = 0.80, 95% CI 0.72–0.88), but the mastectomy conversion rate was similar after OBCS (3.2%) and BCS (3.7%) (p = 0.11) [13]. Mastectomy conversion rates were lower after volume displacement and reduction procedures (OR 0.69, 0.58–0.84) [13], maybe due to more generous excision volumes and margins with these types of procedures.

Compared to mastectomy alone, OBCS may have increased local recurrence-free survival, but again the evidence is very uncertain (HR 0.55, 95% CI 0.34 to 0.91; 2 studies, 4713 participants; very low-certainty evidence) [12]. Nonetheless, data is lacking about post-mastectomy RT and its contribution in the mastectomy group, whereas OBCS is usually accompanied by RT. For OBCS compared to mastectomy with reconstruction procedures, there were no clear differences in local recurrence-free survival (HR 1.37, 95% CI 0.72 to 2.62; 1 study, 3785 participants; very low certainty evidence). Disappointingly, OBCS and breast reconstruction are procedures that aim to improve patients' satisfaction with body image satisfaction, yet, the Cochrane review indicates, that these outcomes were poorly evaluated in the studies [12].

OBCS is typically applied in case of unfavourable tumour/breast volume ratio when mastectomy and/or primary systemic therapy are not indicated for oncological considerations (e.g., inflammatory breast cancer which mandates modified radical mastectomy), including multifocal and multicentric tumours if the procedure will allow resection with free margins [14]. Other considerations of the OBCS approach are challenging locations of the tumour within the breast (e.g., the lower pole) or in case of patient preference, especially as OBCS allows for contralateral volume reduction, augmentation or mastopexy to assure symmetry with the aim of meeting patient expectation [14]. Hence, potential advantages of OBCS are achieving sufficient margins, avoiding mastectomy, and avoiding the potential complications of post-mastectomy RT, especially in case of reconstruction, thereby improving overall patient satisfaction [2,4,15–17].

Therefore, our review focuses on OBCS and aims to discuss the challenges and uncertainties in target volume definition after these procedures, to improve RT decisions and encourage multidisciplinary.

1.1. The most important volume for breast RT

The target volume for whole breast radiation includes all breast tissue, consisting mainly of the glandular tissue as the volume that may encompass potential residual tumour cells. The high-risk volume that may possess most residual tumour cells is the volume in proximity to the tumour bed and index quadrant. Following and in agreement with the work of Holland [18], proving sub-clinical multifocality of T1-2 tumours via microscopic analysis of mastectomy specimens, it was demonstrated in several studies that most of the local recurrences (50–82%) occur at the vicinity of the primary tumour [19–22]. Therefore, properly identifying the primary tumour bed is essential for any breast RT planning, as identification of the tumour bed and correct delineation of the tumour bed and its surroundings will allow to assure adequate dose coverage of this volume [7,8]. This is important for avoiding sub-dosing due to geographical misses or due to compromises done in the RT plan to reduce the heart or lung dose [23] in case of whole breast RT alone; for partial breast RT planning [24,25]; or as the volume to receive an additional RT boost dose [9,26,27].

A Delphi consensus recommendation for partial breast RT were recently published by ACROP-ESTRO [28], while the indication for a tumour bed boost vary very much among centres. Tumour bed boost improves local control compared to no tumour bed boost [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.55 to 0.75] in all patients without improving breast cancer survival and at the expense of increased RT-related toxicity [9,26,27]. The absolute benefit of the boost is related to the risk of local recurrence, and a greater gain was suggested in those that have higher risk factors such as younger age (<40 years), higher tumour stage, tumour grade 3, molecular subtype (triple negative), presence of extensive lymphovascular invasion, presence of extensive ductal carcinoma in situ (DCIS), close or positive margins, microinvasion, and lymph node involvement [29,31–35,30,22]. The timeline of local relapse is related to resection margins and tumour features [36].

Nowadays, breast RT is done with CT-based planning, and for modern RT planning it mandates target volume delineation for planning and appreciation of the RT plan. The aim of target volume delineation is not to include the outdated field-encompassed volumes that were encompassed by the 2D-bony landmarks fields [7,8], but rather to define the true target volumes, based on anatomy, histology and in depth understanding of breast cancer biology and therapy including the surgical procedure [7,37,38]. Large RT volumes, high radiation dose, and inhomogeneous dose delivery were shown to increase breast RT-related toxicity [9–11,39].

1.2. Identifying the tumour bed

Early methods for identification of the tumour bed or for boost planning after conventional BCS surgeries (quadrantectomy, lumpectomy), included patients' own recollection of tumour position, preoperative imaging and/or clinical photographs with tumour marked on skin, tattoos over tumour, and surgical notes [35]. Marking the scar (as it was generally above the tumour) and measuring the depth of the tumour beneath the surface of the skin was used in the early days of providing a tumour bed boost. The radiation technique included mainly brachytherapy or a direct electron field directed at the marking (scar, tattoo, etc) with the electron energy decided based on the depth of the lesion on imaging or, more commonly used, of the depth of the surgical clips as measured on the conventional simulator.

After target volume delineation for breast cancer RT was applied with the introduction of CT-based planning, different groups reported the uncertainties in defining the tumour bed after BCS, including the uncertainties in the presence of seroma or surgical clips [40–46]. The review by Beddok and colleagues [46] summarized the different studies reporting intra- and inter-observer variability of tumour bed delineation. The authors noted that preoperative imaging, clips, seroma, and absences of visible coarse breast calcification were factors reducing the tumour bed variability [46]. However, while it might reduce variability, seroma may extend beyond the tumour bed, with migration of the surgical clips, thus not guaranteeing the true location of the tumour bed [43]. Due to the nature of OBCS, the tumour bed may be shifted and redistributed within the neo-breast and introduce significant uncertainties or inability to identify the tumour bed [47].

1.3. Oncoplastic BCS extent of procedure

The definitions of oncoplastic breast surgery vary in the literature with regards to the specimen volume excised or tissue manipulation. Therefore, the American Society of Breast Surgeons (ASBrS) defines OBCS as breast conserving surgery with ipsilateral defect repair using volume displacement and volume replacement techniques with contralateral symmetry surgery as appropriate [14]. The ASBrS classification system defines the OBCS into two types of procedures: volume *displacement* and volume *replacement*. Volume *displacement* entails redistributing of the breast tissue to close the post-resection cavity. This was divided into two levels based on percentage of breast volume excised (level 1 < 20%, and level 2 between 20 and 50%). Volume *replacement* procedures that use tissue from outside the footprint of the breast (autologous tissue or implant) to correct the volume deficit are included in the definition of oncoplastic BCS. This may or may not result in additional breast augmentation/volume reduction from the original volume and may accompany contralateral augmentation/mastopexy [38].

A population-based study of 18,188 patients undergoing BCT, of which OBCS was performed in 5003, showed that the most popular oncoplastic procedure was volume displacement (83.4%), volume reduction was performed in 13.6% and volume replacement in 3.1% of the cases. In patients over 50, rates of secondary interventions, defined as either a re-excision or a tumour bed boost, were similar after BCS and OBCS (16.4% vs. 15.9%; p = 0.430). However, for those patients, a boost was used less often in BCS patients than in patients undergoing OPBS (14.7% vs. 21.2%, p < 0.001), but without information on association with oncoplastic technique [13].

Fig. 1 summarizes the a few of the different types of OBCS. Keeping in mind that each procedure is decided according to tumour location and its distance from the nipple areola complex, the amounts of volume resection, according to size of the lesion, number of lesions, in relation to the breast size and ptosis.

1.4. Target volume after OBCS

OBCS procedures introduce significant uncertainty in the tumour bed location, even if clips are used in a predefined manner [47,48]. Preoperative images may misguide the radiation oncologist in identifying the tumour bed, due to distortion or reposition of the breast anatomy. The mammographic position of the tumour may not directly correlate with the surgical changes seen on planning CT, or the position of the scar (Fig. 1). The tumour bed position can be shifted differently in the same OBCS procedure depending on the volume resected, presence of seroma or bleeding. Clips applied at the level of the tumour bed, on each side of the cavity and at the level of the chest wall prior to tissue manipulation may not accurately represent the tumour bed, and individual surgical clips may displace or migrate in a range of 3.5 cm outside the primary tumour bed [47]. The degree of clip displacement was suggested to occur to a greater degree in inferior pedicle reduction mammoplasty and superior medial pedicle vertical reduction mammoplasty [47]. In axial CT slices for tumour bed delineation after OBCS, a single tumour may thus result in detached high risk volumes (Fig. 2) [47].

Key recommendations for assisting in accurate delineation of the tumour bed after BCS include marking the walls of the surgical cavity at the level of the tumour bed with at least 5 surgical clips prior to tissue rearrangements [42]. Delineation should consider the clips based on their location in relation to the tumour bed (using preoperative imaging, operative note and pathology report as references). The target volume should take into account tumour size, as the breast tissue around it is "at risk" to harbour residual foci, as well as excision margins according to its orientation in all directions, if available. The clinical target volume is considered including 1.5 cm of breast tissue surrounding the primary tumour for a boost, and 2 cm for partial breast RT [Fig. 3]. Whereas the tumour bed localization might be difficult to identify after classical

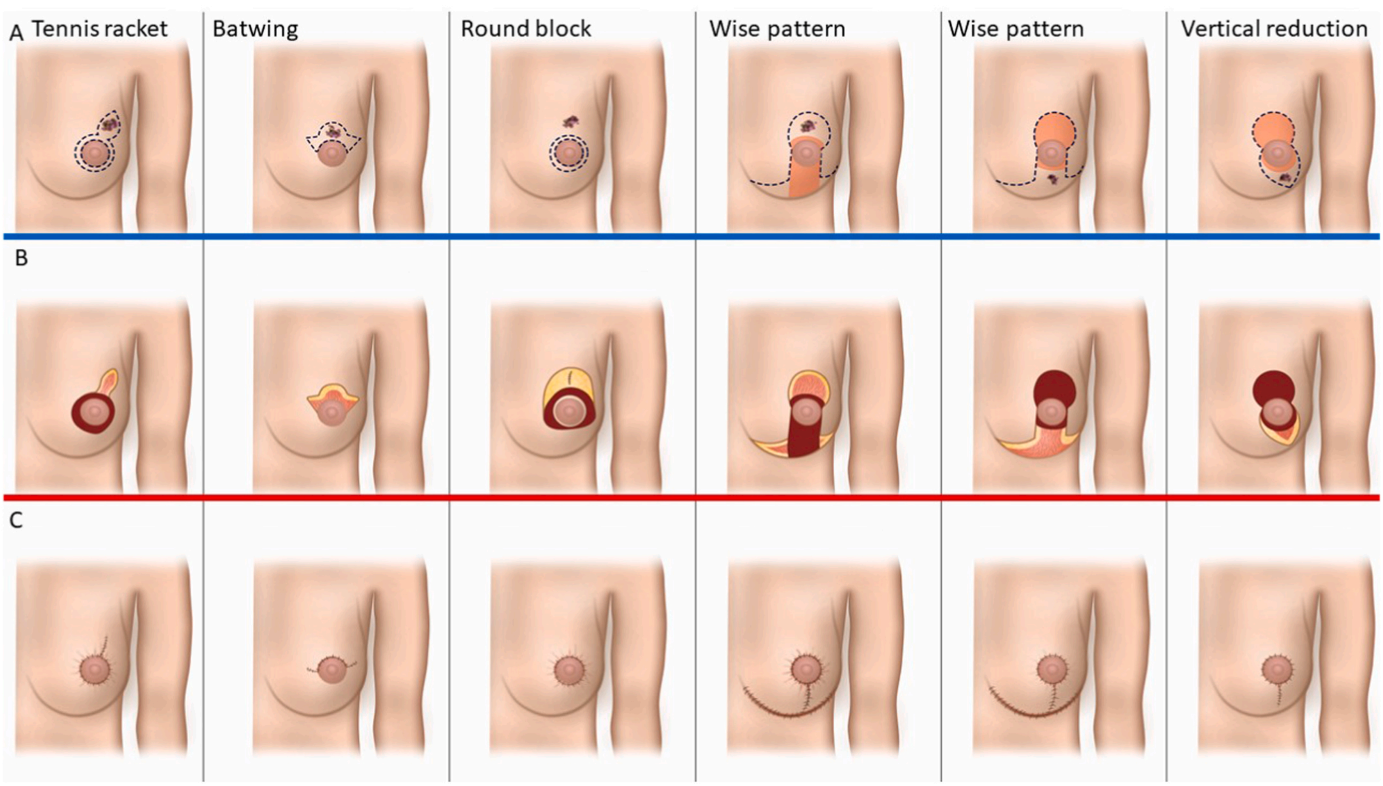

Fig. 1. Selected illustrations of oncoplastic procedures, the different types are selected according to size and location of lesion and tumour to breast ratio, degree of ptosis, size of the nipple-areola and other considerations. The columns are showing the same type of procedure, the rows illustrate the different phases of surgery. (A) preoperative planning according to tumour location, (B) the lumpectomy and exposure of tissues and de-de-epithelization, (C) the final outcomes, nipple areola transposition, and scar. **Lateral Mammoplasty** (Tennis racket) method, often used for tumours located in the upper outer and lower outer quadrants but it can be used for other quadrants as well, with the cost of aesthetics as the tennis racket may induce scar retraction and unintended displacement of the nipple-areola complex. **Batwing mastopexy (**inverted V or omega plasty), the lumpectomy cavity defect is closed by pulling up the inferior breast tissue and suturing the layers together. It is often used for lesions in the upper central breast near the nipple. The procedure allows to hide part of the scar at the border of the areola. **The round block** technique in patients with small to moderate-sized breasts without/limited degree of ptosis. The tissue between the two incisions is de-epithelialized. The scars are perimamillary and well hidden, and in the case of a large areola, a smaller neo-areola may be created. A symmetrisation procedure should be considerd. **Wise pattern (inverted T),** two figure first is inferior based pedicle and superior based pedicle. Superomedial might be used as well. Technique in patients with moderate to large sized breasts with ptosis, lumpectomy cavity defect moderate to large. **Vertical pattern** technique in patients with moderate sized breasts and ptosis. The lumpectomy defect and ptosis are limited compared to wise pattern. The breast tissue is pushed medially and laterally against a vertical line, the medial and lateral incision line is determined as the area to be resected. After the tumour resection, the dermal pedicle de-epithelialized, is elevated and the parenchymal tissue inside the incision line is removed.

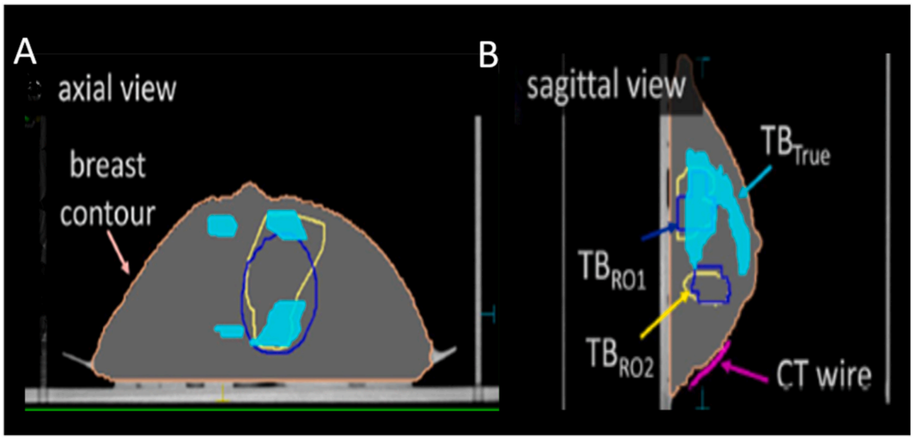

Fig. 2. Identification of the true tumour bed (TB) on a phantom breast after oncoplastic breast surgery. A) axial CT-slice; B) sagittal view showing how the TB can be not connected.
Modified from Aldosary, G., Caudrelier, JM., Arnaout, A. et al. Can we rely on surgical clips placed during oncoplastic breast surgery to accurately delineate the tumor bed for targeted breast radiotherapy? Breast Cancer Res Treat 186, 343–352 (2021). https://doi.org/10.1007/s10549-020-06086-3.

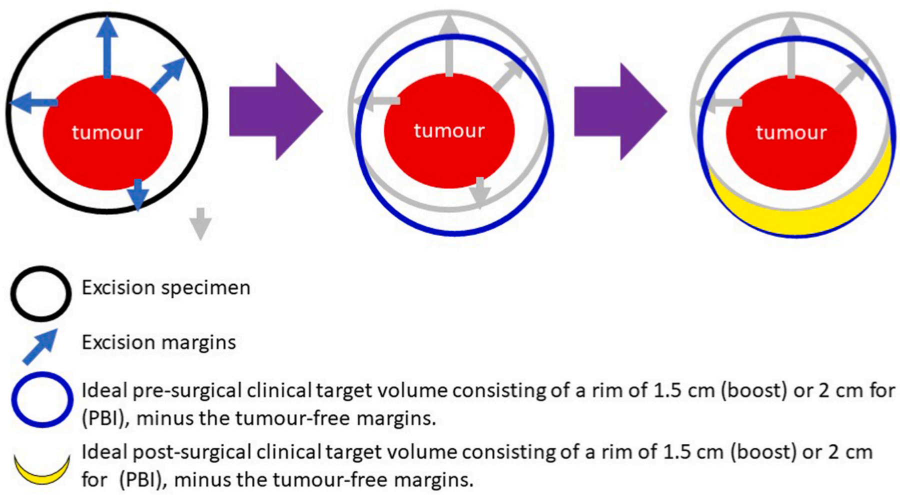

Fig. 3. Ideal target volume, accounting for excision margins.

lumpectomy, it is most often even more difficult after OBCS, where the surgical changes are more extensive and/or clips might be misleading [43,48,49]. Regrettably, localization of the tumour bed in the setting of OBCS is not well defined in studies [50], and currently it is impossible to make firm recommendations according to each type of OBCS. Only a cautionary remark to the radiation oncology community that OBCS produces uncertainties, and overconfidence in surgical clips may result in erroneous location of the high-risk volume, and uncertainty should not be compensated by enlarging the volume of the boost or increasing the dose. The figures below show two cases for whom a boost was

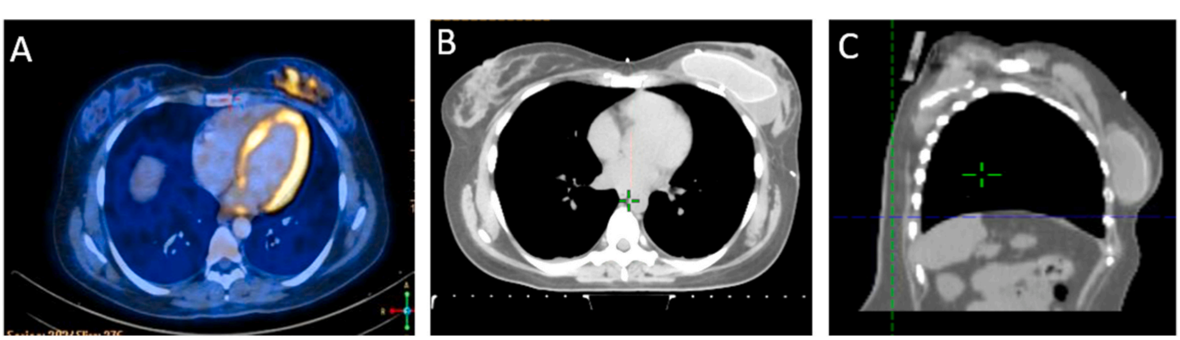

Fig. 4. A) Axial view of FDG-PET CT done at time of diagnosis, showing FDG uptake at the left breast. B) Axial view of postoperative radiation planning CT showing a volume replacement procedure of the left breast. A tumour bed boost was indicated because of patients young age (35 years) and grade 3, highly proliferative invasive tumour (high Ki-67). B) Sagittal view of radiation planning CT shows that if a boost was planned to include the volume encompassing the implant, most of the breast would have received the high dose. Therefore, a boost was omitted in this case.

omitted due to inability to properly identify a not-excessively large tumour bed (Fig. 4a,b,c Fig. 5).

Therefore, it is our recommendation that patients who undergo OBCS are not good candidates for partial breast RT, unless a limited volume displacement procedure was performed and the tumour bed can be identified accurately with appropriate margins. In these patients, the IMPORT-LOW planning with two doses of 40.05 Gy in 15 fractions for the high-risk region and 36 Gy for the remaining breast volume can be considered to compensate uncertainties, even though this was not part of the trial objectives, as it may reduce toxicity compared to whole breast RT to the full dose [24].

In high-risk breast cancer patients, in whom the indication for a boost is known prior to surgery, the surgical approach should be pre-planned bearing in mind of this indication and the uncertainty in planning the boost. Therefore, the value of discussing the cases within a multidisciplinary team is highly important to plan the approach. Breast surgery expertise is important, and the surgical procedure should attempt for generous margins, clip the surgical cavity walls prior to surgical tissue manipulation (even though there are pitfalls for this approach), and record in a note the possible location and shifting of the tumour bed according to the surgical manipulation. Obtaining a radical resection with tumour free margins has high priority in all surgical procedures but is of specific value in OBCS. A radical resection with sufficient margins which might be more feasible in OBCS (e.g., 2 cm margin) will even preclude the need for a boost in a high-risk breast cancer as the clinical target volume is resected in this case. Therefore, it is essential to have appropriate expertise in planning these surgeries to allow for suitable oncological and aesthetic outcomes. Uncertainties in orientation of the margins in a non-radical resection, with positive or close margins, that precludes re-excision, needs to consider as well the uncertainties in tumour bed definition in these cases. Surgical changes seen on planning CT, and clips may represent the surgical cavity but not the primary tumour bed or the high-risk volume. Re-excision is often challenging due to uncertainties, but uncertainties apply also for identification of the tumour bed for a RT boost. Therefore, to avoid a mastectomy due to positive margins, or large boost volumes, pre-surgery planning mandates expertise and should be done carefully within a multidisciplinary group.

It is important that the surgeons are familiar with the concept of tumour bed delineation and the different views of the planning CT, and work together with the radiation oncologists to understand the surgical procedure and the principle of the tumour bed volume [48]. For this purpose, the annual Aarhus Workshop in Breast Surgery (Denmark) in 2023 dedicated a multidisciplinary session to tackle the uncertainties of OBCS and tumour bed delineation.

Indications for a boost should be defined for truly high-risk patients, particularly as with screening programs and new systemic therapies, the local recurrence rates are significantly lower compared to early reports [51]. Current recommendation for tumour bed boost as recommended by the Danish Breast Cancer Group (DBCG) include age younger than 50 (regardless of margin status from invasive carcinoma), and in women >50 with distance from DCIS/pleomorphic LCIS and/or invasive carcinoma of less than 2 mm to the surgical margin. The ESTRO breast cancer focus group has set a goal to achieve a consensus on the indication for a boost, based on currently available evidence from recent trials.

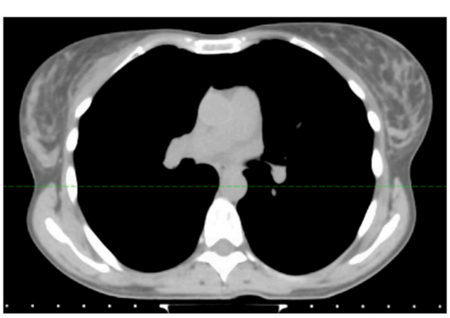

Fig. 5. Axial view of radiation planning CT showing a left breast volume displacement procedure with mammoplasty and right breast mammoplasty. A tumour bed boost was indicated because of patients young age (39 years), grade 3, highly proliferative invasive tumour (high Ki-67) and close margin of 0.8 mm. Tumour bed boost was omitted due to inability to identify the tumour bed: dense glandular tissue, no visualisation of the tumour bed on CT and the nature of the surgical procedure.

Even though data is lacking about its effect, OBCS aims to improve patient satisfaction around aesthetics without compromising oncological outcomes in tumours for which conventional BCS will result in deformity (more than 10% of breast or unfavourable location) [4,15,17,52]. Therefore, it seems reasonable to attempt OBCS, and avoid mastectomy, which often leads to reconstruction and RT-related complications in many patients [16]. Nevertheless, these surgeries mandate careful preoperative planning, reviewing the imaging for extent of disease, calcifications, the need to resect part of the skin, and possible other technical interventions to assure a radical resection. Preoperative evaluation should consider the benefit of primary systemic therapy, both chemotherapy-based or endocrine therapy combined with CDK4/6i, to reduce the tumour size and allow for standard lumpectomy if feasible or to facilitate resection with clear margins. The location of the tumour, number of lesions, extent of calcification and patient's body habitus, size and configuration of the breasts are paramount for choosing the correct procedure.

1.5. *Future planning & recommendations*

Preoperative boost [NCT04871516], intraoperative boost [53], or a ring shape boost (around the flap used for volume replacement) [48] were also proposed as a possible approach in OBCS, but should be evaluated in prospective trials with proper reporting of tumour bed definition, radiation dose and volume and radiation planning [48,54]. The use of breast MRI and MRI-based planning requires further exploration if it aids to truly identify the tumour bed (rather than the surgical cavity) in the presence of OBCS [55,56]. Similarly, the use of new products for tumour bed marking such as 3-dimensional bioabsorbable tissue marker should be further explored in a prospective trial in the context of OBCS [57] including migration of the marker compared to surgical clips – always keeping in mind the huge pitfall that the surgical cavity rarely, if ever, accurately represents the primary tumour bed. In addition, a new artificial intelligence based tool is currently being developed and evaluated in the CINDERELLA trial [NCT05196269] [58] to inform patients on the aesthetic outcomes of the different breast cancer surgeries in aim to improve patient satisfaction with the outcomes of locoregional therapy.

It is our recommendation, that retrospective or prospective studies reporting the outcomes of OBCS need to indicate details about the RT applied and specify if a tumour bed boost was given, including the method of tumour bed marking and boost planning to evaluate efficacy and to provide evidence to support guidelines.

As these procedures aim to provide a better aesthetic outcome after breast cancer surgery, it is our responsibility to assure their safety. The procedure should be planned to ensure radical resection with clear margins, and sufficient margins in high-risk cases, to reduce the need for a boost merely because close-positive margins or the need for subsequent mastectomy, because of uncertainties that could be avoided. In cases that tumour bed boost is strongly indicated, the radiation oncologist and the surgeon must work together to accurately define the target volumes.

Credit statement

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data: OKP (2) drafting the article or

revising it critically for important intellectual content: all (3) final approval of the version to be submitted: all.

No COI: all authors.

AI and AI-assisted technologies not used to produce this manuscript.

References

[1] https://www.cancerresearchuk.org/health-professional/cancer-statistics/treatment. https://www.cancerresearchuk.org/health-professional/cancer-statistics/treatment.

[2] Clough KB, Cuminet J, Fitoussi A, et al. Cosmetic sequelae after conservative treatment for breast cancer: classification and results of surgical correction. Ann Plast Surg 1998;41:471–81.

[3] Clough KB, Massey EJ, Mahadev GK, et al. Oncoplastic technique for the elimination of the lateral "dog ear" during mastectomy. Breast J 2012;18:588–90.

[4] Clough KB, Lewis JS, Couturaud B, et al. Oncoplastic techniques allow extensive resections for breast-conserving therapy of breast carcinomas. Ann Surg 2003;237: 26–34.

[5] Smeele HP, Van der Does de Willebois EML, Eltahir Y, et al. Acceptance of contralateral reduction mammoplasty after oncoplastic breast conserving surgery: a semi-structured qualitative interview study. Breast 2019;45:97–103.

[6] Kaidar-Person O, Hermann N, Poortmans P, et al. A multidisciplinary approach for autologous breast reconstruction: a narrative (re)view for better management. Radiother Oncol 2021;157:263–71.

[7] Kaidar-Person O, Offersen BV, Boersma L, et al. Tricks and tips for target volume definition and delineation in breast cancer: lessons learned from ESTRO breast courses. Radiother Oncol 2021;162:185–94.

[8] Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1. Radiother Oncol 2016;118:205–8.

[9] Poortmans PM, Collette L, Horiot JC, et al. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. Radiother Oncol 2009;90:80–5.

[10] Thomsen MS, Alsner J, Nielsen HM, et al. Volume matters: breast induration is associated with irradiated breast volume in the Danish Breast Cancer Group phase III randomized Partial Breast Irradiation trial. Radiother Oncol 2022;177:231–5.

[11] Donovan E, Bleakley N, Denholm E, et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 2007;82:254–64.

[12] Nanda A, Hu J, Hodgkinson S, et al. Oncoplastic breast-conserving surgery for women with primary breast cancer. Cochrane Database Syst Rev 2021;10: Cd013658.

[13] Heeg E, Jensen MB, Holmich LR, et al. Rates of re-excision and conversion to mastectomy after breast-conserving surgery with or without oncoplastic surgery: a nationwide population-based study. Br J Surg 2020;107:1762–72.

[14] Chatterjee A, Gass J, Patel K, et al. A consensus definition and classification system of oncoplastic surgery developed by the American society of breast surgeons. Ann Surg Oncol 2019;26:3436–44.

[15] Chand ND, Browne V, Paramanathan N, et al. Patient-reported outcomes are better after oncoplastic breast conservation than after mastectomy and autologous reconstruction. Plast Reconstr Surg Glob Open 2017;5:e1419.

[16] de Boniface J, Coude Adam H, Frisell A, et al. Long-term outcomes of implant-based immediate breast reconstruction with and without radiotherapy: a population-based study. Br J Surg 2022;109:1107–15.

[17] Weber WP, Shaw J, Pusic A, et al. Oncoplastic breast consortium recommendations for mastectomy and whole breast reconstruction in the setting of post-mastectomy radiation therapy. Breast 2022;63:123–39.

[18] Holland R, Veling SH, Mravunac M, et al. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer 1985;56:979–90.

[19] Luini A, Gatti G, Zurrida S, et al. The evolution of the conservative approach to breast cancer. Breast 2007;16:120–9.

[20] Chang JS, Byun HK, Kim JW, et al. Three-dimensional analysis of patterns of locoregional recurrence after treatment in breast cancer patients: validation of the ESTRO consensus guideline on target volume. Radiother Oncol 2017;122:24–9.

[21] Fowble B, Solin LJ, Schultz DJ, et al. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. Int J Radiat Oncol Biol Phys 1990;19:833–42.

[22] Botteri E, Bagnardi V, Rotmensz N, et al. Analysis of local and regional recurrences in breast cancer after conservative surgery. Ann Oncol 2010;21:723–8.

[23] Raj KA, Evans ES, Prosnitz RG, et al. Is there an increased risk of local recurrence under the heart block in patients with left-sided breast cancer? Cancer J 2006;12: 309–17.

[24] Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017;390:1048–60.

[25] Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: long-term results of the randomized phase III APBI-IMRT-Florence trial. J Clin Oncol 2020;38: 4175–83.

[26] Poortmans PM, Collette L, Bartelink H, et al. The addition of a boost dose on the primary tumour bed after lumpectomy in breast conserving treatment for breast cancer. A summary of the results of EORTC 22881-10882 "boost versus no boost" trial. Cancer Radiother 2008;12:565–70.

[27] Kindts I, Laenen A, Depuydt T, et al. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane Database Syst Rev 2017;11:Cd011987.

[28] Meattini I, Becherini C, Boersma L, et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol 2022;23:e21–31.

[29] Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–32.

[30] Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.

[31] Chang JS, Lee J, Chun M, et al. Mapping patterns of locoregional recurrence following contemporary treatment with radiation therapy for breast cancer: a multi-institutional validation study of the ESTRO consensus guideline on clinical target volume. Radiother Oncol 2018;126:139–47.

[32] Vrieling C, van Werkhoven E, Maingon P, et al. Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC boost vs No boost trial: a randomized clinical trial. JAMA Oncol 2017;3:42–8.

[33] Vrieling C, van Werkhoven E, Maingon P, et al. Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC boost vs No boost trial: a randomized clinical trial. JAMA Oncol 2017;3:42–8.

[34] Goldberg M, Parpia S, Rakovitch E, et al. Long-term outcomes and effects of hypofractionated radiotherapy in microinvasive breast cancer: analysis from a randomized trial. Breast 2023;68:189–93.

[35] Jalali R, Singh S, Budrukkar A. Techniques of tumour bed boost irradiation in breast conserving therapy: current evidence and suggested guidelines. Acta Oncol 2007;46:879–92.

[36] Colleoni M, Sun Z, Price KN, et al. Annual hazard rates of recurrence for breast cancer during 24 Years of follow-up: results from the international breast cancer study group trials I to V. J Clin Oncol 2016;34:927–35.

[37] Tramm T, Christiansen P, Offersen BV, et al. Superficial margins in skin sparing and nipple sparing mastectomies for DCIS: a margin of potential concern. Radiother Oncol 2021;61:177–82.

[38] Tramm T, Kaidar-Person O. Optimising post-operative radiation therapy after oncoplastic and reconstructive procedures. Breast 2023;69:366–74.

[39] Kaidar-Person O, Gentilini O, Poortmans P. Not only volumes matter for breast radiation therapy. Radiother Oncol 2022;177:236–7.

[40] Guo B, Li J, Wang W, et al. Interobserver variability in the delineation of the tumour bed using seroma and surgical clips based on 4DCT scan for external-beam partial breast irradiation. Radiat Oncol 2015;10:66.

[41] Ding Y, Li J, Wang W, et al. A comparative study on the volume and localization of the internal gross target volume defined using the seroma and surgical clips based on 4DCT scan for external-beam partial breast irradiation after breast conserving surgery. Radiat Oncol 2014;9:76.

[42] Kirby AN, Jena R, Harris EJ, et al. Tumour bed delineation for partial breast/breast boost radiotherapy: what is the optimal number of implanted markers? Radiother Oncol 2013;106:231–5.

[43] Yang Z, Chen J, Hu W, et al. Planning the breast boost: how accurately do surgical clips represent the CT seroma? Radiother Oncol 2010;97:530–4.

[44] Wang W, Li J, Xing J, et al. Analysis of the variability among radiation oncologists in delineation of the postsurgical tumor bed based on 4D-CT. Oncotarget 2016;7: 70516–23.

[45] Giezen M, Kouwenhoven E, Scholten AN, et al. MRI- versus CT-based volume delineation of lumpectomy cavity in supine position in breast-conserving therapy: an exploratory study. Int J Radiat Oncol Biol Phys 2012;82:1332–40.

[46] Beddok A, Kirova Y, Laki F, et al. The place of the boost in the breast cancer treatment: state of art. Radiother Oncol 2022;170:55–63.

[47] Aldosary G, Caudrelier J-M, Arnaout A, et al. Can we rely on surgical clips placed during oncoplastic breast surgery to accurately delineate the tumor bed for targeted breast radiotherapy? Breast Cancer Res Treat 2021;186:343–52.

[48] Garreffa E, Hughes-Davies L, Russell S, et al. Definition of tumor bed boost in oncoplastic breast surgery: an understanding and approach. Clin Breast Cancer 2020;20:e510–5.

[49] Aldosary G, Caudrelier JM, Arnaout A, et al. Can we rely on surgical clips placed during oncoplastic breast surgery to accurately delineate the tumor bed for targeted breast radiotherapy? Breast Cancer Res Treat 2021;186:343–52.

[50] Schaverien MV, Stallard S, Dodwell D, et al. Use of boost radiotherapy in oncoplastic breast-conserving surgery - a systematic review. Eur J Surg Oncol 2013;39:1179–85.

[51] Bosma SCJ, Hoogstraat M, van Werkhoven E, et al. A case-control study to identify molecular risk factors for local recurrence in young breast cancer patients. Radiother Oncol 2021;156:127–35.

[52] Behluli I, Le Renard PE, Rozwag K, et al. Oncoplastic breast surgery versus conventional breast-conserving surgery: a comparative retrospective study. ANZ J Surg 2019;89:1236–41.

[53] Sedlmayer F, Reitsamer R, Wenz F, et al. Intraoperative radiotherapy (IORT) as boost in breast cancer. Radiat Oncol 2017;12:23.

[54] Kaidar-Person O, Poortmans P. Partial breast irradiation with intraoperative radiotherapy in the ELIOT trial. Lancet Oncol 2021;22:e294.

[55] Lowrey N, Koch CA, Purdie T, et al. Magnetic resonance imaging for breast tumor bed delineation: computed Tomography comparison and sequence variation. Adv Radiat Oncol 2021;6:100727.
[56] Dong Y, Liu Y, Chen J, et al. Comparison of postoperative CT- and preoperative MRI-based breast tumor bed contours in prone position for radiotherapy after breast-conserving surgery. Eur Radiol 2021;31:345–55.
[57] Kaufman CS, Cross MJ, Barone JL, et al. A Three-dimensional bioabsorbable tissue marker for volume replacement and radiation planning: a multicenter study of surgical and patient-reported outcomes for 818 patients with breast cancer. Ann Surg Oncol 2021;28:2529–42.
[58] Kaidar-Person O, Antunes M, Cardoso JS, et al. Evaluating the ability of an artificial-intelligence cloud-based platform designed to provide information prior to locoregional therapy for breast cancer in improving patient's satisfaction with therapy: the CINDERELLA trial. PLoS One 2023;18:e0289365.