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NARRATIVE REVIEW

Adjuvant radiation treatment of the surgical bed in breast cancer: who, when and how to do it: A narrative review

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Abtract

Introduction: Currently there are discrepancies regarding the indication, dose, technique and contouring of the superimpression or increase in irradiation dose on the surgical bed in adjuvant treatment in breast cancer.

Pu rpose of the review : The objective of the review is to present the available evidence on superimposing the surgical bed in the treatment of breast cancer. We carried out a bibliographic review in MEDLINE pubmed, 61 studies published between January 2000 and January 2022 were analyzed.

Recent findings : Superimpression on the surgical bed in the breast improves local control in those patients with high-risk elements. The different techniques available are oncologically equivalent. The delineation of the treatment target should be guided by the surgical clips.

Conclusions : The indication of this treatment must be evaluated by the radiotherapy oncology services, defining their protocols and action algorithms.

Keywords :
MESH: Adjuvant Radiotherapy, Breast Neoplasms, Inflammatory Neoplasms of the Breast.

Introduction

Breast cancer worldwide ranks first in incidence and mortality in women, with 9.2 million new cases (24.5%) and 4.4 million deaths (15.5%) per year [1].

Currently for the initial stages, the local treatment is conservative surgery and radiotherapy to the breast with the nodal regions as indicated. Adjuvant radiation therapy decreases the 10-year risk of first locoregional or distant recurrence from 35% to 19.3% (P< 0.00001), as well as lowers the 15-year risk of breast cancer mortality from 25.2% to 21.4% (P =0.00005).

This translates into a halving of the risk of local recurrence and a sixth of the specific mortality rate [2].

There is scientific evidence supporting boosting or increasing the radiation dose to the tumor bed, which reduces the risk of local recurrence [3-5].

Currently we find differences in terms of indication, dose, fractionation and technique to perform it. Therefore, our objective is to carry out a bibliographic review in order to present the available evidence regarding the boosting of the tumor bed after conservative surgery in breast cancer.

Materials and methods

Study design

This study was based on a bibliographic review. We searched for scientific literature published in MEDLINE PubMed, assessing: technique, indication, dose and contouring. Articles in English, in the period between January 2000 and January 2022. The selected studies were those that evaluated adult women with invasive or in situ breast cancer (DCIS), who received conservative surgery and adjuvant treatment with full-length radiotherapy. the breast (Whole-breast irradiation WBI) with superimposition to the tumor bed or accelerated partial breast irradiation (APBI). We included the following MeSH terms and “text words” in the different bibliographic searches: “adjuvant radiotherapy breast cancer”, “breast tumor bed”, “radiotherapy treatment”; “lumpectomy cavity”, “contouring OR delineation OR localization”, “radiation techniques”, “brachytherapy OR phototherapy OR electron therapy OR Intraoperative radiation therapy”; “dose fractionation, radiotherapy”, “standard OR conventional radiotherapy fractionation OR hypofractionation, radiotherapy dose”; “radiotherapy treatment indication”. Of the total number of studies found, 61 articles were included and analyzed.

Results

Indication of boost in tumor bed

The majority of local relapses in breast cancer arise at the level of the tumor bed and in the vicinity of it, which is why it was justified to propose a dose escalation (Figure 1).

Retrospective and prospective studies have shown that this dose escalation to the tumor bed decreases the risk of local relapse [6, 7] and improves relapse-free survival [8].

Polgar et al. analyzed 207 patients treated between 1995 and 1998, with a mean follow-up of 5.3 years, finding a lower rate of crude local recurrence, 6.7% vs 15.5%, with and without boost, respectively. The 5-year probability of local tumor control was 92.7% vs 84.9% (p=0.049) and disease-free survival 76.6% vs 66.2% (P =0.044) [6]. The EORTC 22881-10882 study published in 2014 included 5,318 patients randomized to receive or not a 16 Gy boost. With a mean follow-up of 17.2 years, he observed a cumulative incidence of local relapse of 16.4% vs 12% with and without boost, respectively. No difference in survival (59.7% vs 61.1%) [5] (See figure 2).

In a Cochrane systematic review published in 2017, they included 5 randomized trials, for a total of 8325 patients. Better local control was evidenced in the group that received boost vs. no boost in the tumor bed, HR 0.64, (95% CI 0.55 - 0.75) (Figure 3).

Regarding the recommendations postulated by the different oncology and radiotherapy societies, we have the following information.

The NCCN recommends boosting in the tumor bed in patients at high risk of recurrence, with a fractionation of 10-16 Gy into 4-8 fractions [8].

The Royal College of Radiologists suggests its use in women ≤50 years of age. Those over 50 years of age with high pathological risk factors (histological grade 3 and/or extensive ductal carcinoma in-situ) would also be highly indicated for boosting. It recommends as a technique the use of photons with intensity modulated radiation therapy (Intensity-modulated radiation therapy IMRT), with image-guided radiation therapy (IGRT), including it simultaneously with the planning of full breast treatment (simultaneous integrated boost SIB) [9].

The American Society for Radiation Oncology (ASTRO) recommends superimpression in women ≤50 years of age, between 51-70 years of age with high tumor grade or positive margin. It could be omitted in women > 70 years with low/intermediate grade, positive hormone receptors and a wide negative margin (≥ 2 mm). The fractionation scheme and its indication should be independent of that used in whole breast irradiation [10].

The European Society for Medical Oncology (ESMO) suggests the indication of boosting with radiotherapy in patients ≤50 years, histological grade 3, extensive ductal carcinoma in-situ, lymphovascular invasion, positive margin [11].

St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2021, does not have unified criteria, most of the panelists recommend in high-risk situations: young women (<50 years), histological grade 3, her2 positive, triple negative and extracapsular lymph node involvement. Others, on the other hand, indicate in all patients with conservative surgery [12].

GEC-ESTRO Breast Cancer Working Group 2017 recommends the use of boosting the tumor bed at doses ≥16 Gy EQD2, in those patients with: positive margin or under ≤ 40 years of age with at least one of the following major risk factors: near margin (<2 mm) extensive or triple negative intra-ductal component. The intermediate risk category recommends boosting with 10 - 16 Gy EQD2, includes patients under ≤ 40 years without major risk factors, between 40 - 50 years, ≥ 50 years with one or more of the following risk factors: margin close (<2 mm), tumor size >3 mm, extensive intraductal component, lymphovascular invasion, multicentric or multifocal, triple negative, nodal involvement, or residual tumor disease after neoadjuvant ther- apy. Patients who meet all of the following criteria, ≥ 50 years, tumor ≤ 3 cm, unifocal and unicentric, no lymph node involvement, negative margin > 2 mm, no lymphovascular invasion or extensive intraductal component, and no triple negative may be omitted [13].

Contouring of the tumor bed

The delimitation of the contours has been done using the information available in the clinical history, tumor location, fiducials, scar, images (ultrasound, mammography, tomography, MRI) and surgical clips [14-17].

Figure 1 . Event rates for any first recurrence (locoregional or distant) (% per year) and ratios of recurrence rates for various factors, considered separately, for years 0-9 in women with pathologically node-negative disease (n=7287) Early Breast Cancer Investigators Collaborative Group (EBCTCG). Effect of radiation therapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomized trials. The lancet. 2011c; 378 (9804): 1707–1716.

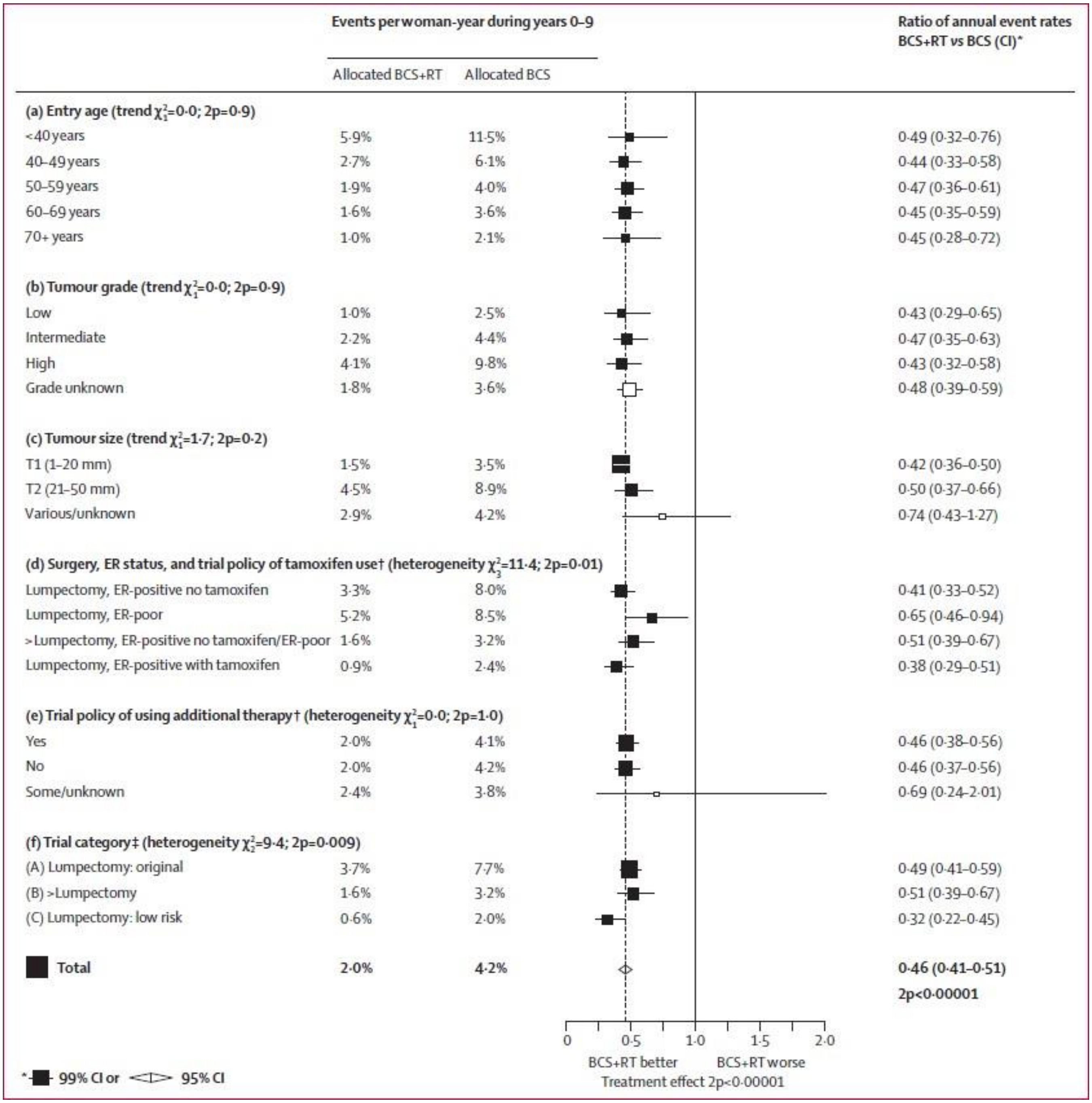
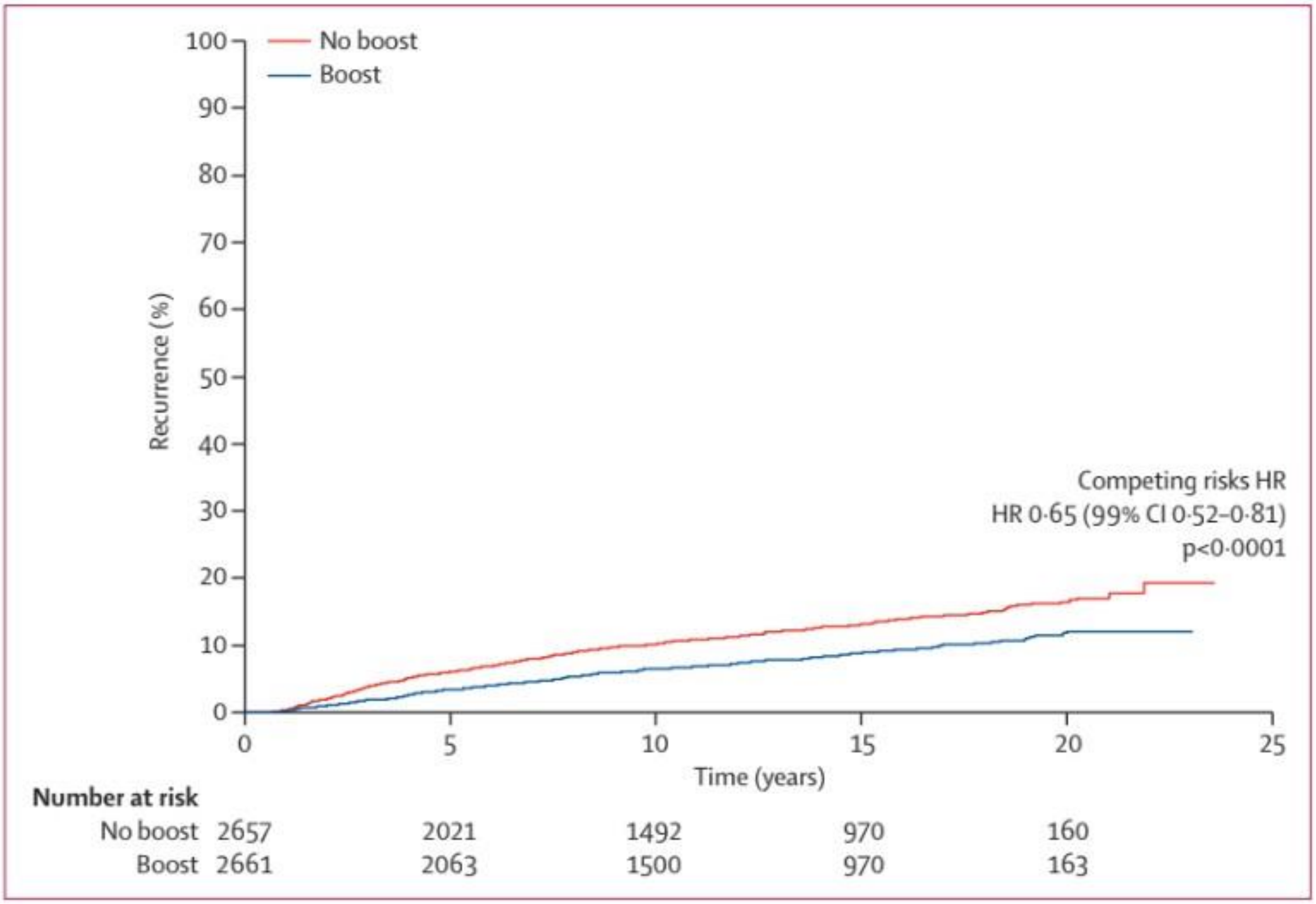
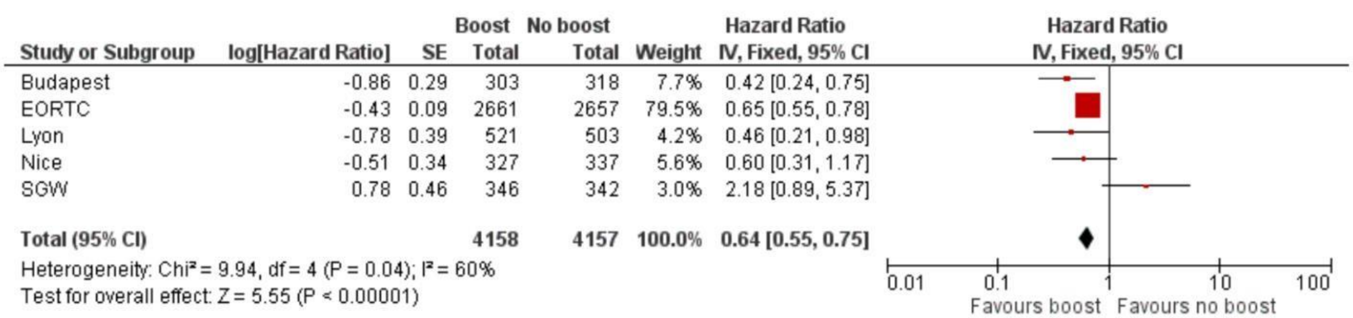


Figure 2. Hazard Ratio of Recurrence in ipsilateral breast tumor.



Bartelink H. Impact of higher radiation dose on local control and survival in breast -conserving therapy of early breast cancer: 10-year results of the randomized trial EORTC 22881-10882 boosted versus unboosted. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2007; 25(22): 3259–3265.

Figure 3. Forest plot diagram for the comparison of local control between overprinting vs not overprinting



Kindts I, Laenen A, Depuydt T, Weltens C. Booster radiation therapy to the tumor bed for women after breast-conserving surgery. Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD011987.

There is great variability between radiation oncologists in the delimitation of the tumor bed, when tomography is used without the presence of surgical clips [15].

It has been shown that the use of at least 4 surgical clips (radial, superficial, and deep) improves the compliance index, interobserver variability, margins required to correctly cover the tumor bed, and precision in its delimitation [16].

We found that when ≥5 clips are used in the bed, the tomography clinical target volume (CTV) is consistent with that of the surgical specimen. Comparing the correlation between the vol- umes of the surgical bed delimited by pre-operative resonance, tomography with clips, patho- logical GTV (gross tumor volume) and surgical specimen GTV. Neither the volume of the to- mography nor the volume of the piece correlate with the volume of the resonance [18, 19], nor did we find relevant clinical differences in the interobserver variability [18] (Figure 4).

Performing a second simulation CT for bed re-planning decreases the size of the seroma, the volume of the superimpression and the doses to organs at risk [20, 21].

In those patients who for some reason were not clipped during surgery, MRI improves visualization of post-surgical changes, reduces interobserver variability, and improves the accuracy of CTV [20] (Figure 5).

A significant improvement in the interobserver compliance rate is obtained using fat-suppressed T1-weighted MRI compared with sham tomography [22 - 25].

The "Canadian Cancer Research Journal Oncology 2020", made a consensus on the location of the tumor bed, including 20 experts, who recommend the following: surgical clips should be placed along the 4 lateral walls of the cavity, plus 1–4 clips on the posterior margin if necessary (avoid its use outside the bed); the preparation of surgical reports to precisely guide the radiation oncologists as soon as; to the size, location of the tumor, the size of the defect and specific data of the procedure (type, tissue rotation, coordinates of the clips) [22].

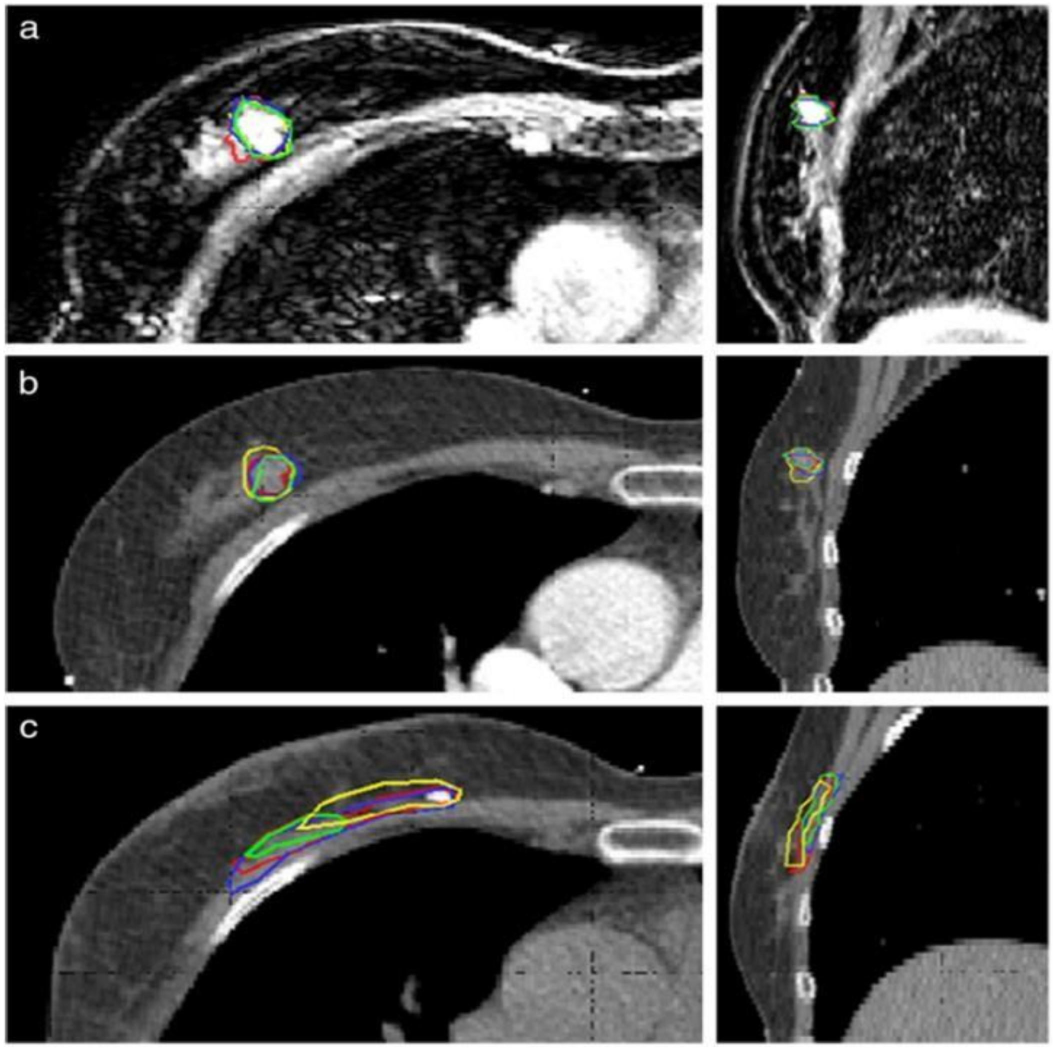
Aldosary G. et al. used breast phantoms which received different oncoplastic surgery techniques, and analyzed the similarity coefficient, Hausdorff distance, and supra and infra contoured volumes. Finding that the clips were significantly displaced from the initial quadrant (± 3.5 cm). No differences were found between and within radiotherapists in bed contouring; but there were significant differences when compared with the "true bed volume" (defined by the authors). Concluding that using only the clips does not allow the precise localization of the tumor bed, therefore its delimitation is challenging [24].

Techniques, dosage and fractionation

Regarding the comparison of external radiotherapy with photons, 16 Gy electrons in 8 fractions, or 15 Gy interstitial brachytherapy with iridium 192, no difference was found in terms of rate or degree of fibrosis, local control, metastasis-free survival, or overall survival [26-29].

No differences were found between boosting with electrons or brachytherapy, when evaluating the aesthetic results at 2 years and those reported by patients on quality of life and body image [30]. Intraoperative boost (with portable accelerators, 10-12 Gy single fraction, electron beam) is a possible, reliable treatment, has an acceptable acute and chronic toxicity rate, as well as an excellent local control rate [31-33] (Figure 6).

Figure 4. GTV delineation by 4 different radiotherapists, transversal and sagittal tomographic sections. a) Preopera- tive with resonance, b) Preoperative with tomography and c) Postoperative with tomography.



Den Hartogh MD, et al. Magnetic resonance imaging and computed tomography for preoperative target volume delineation in breast conservation therapy. 2014; 9(1).

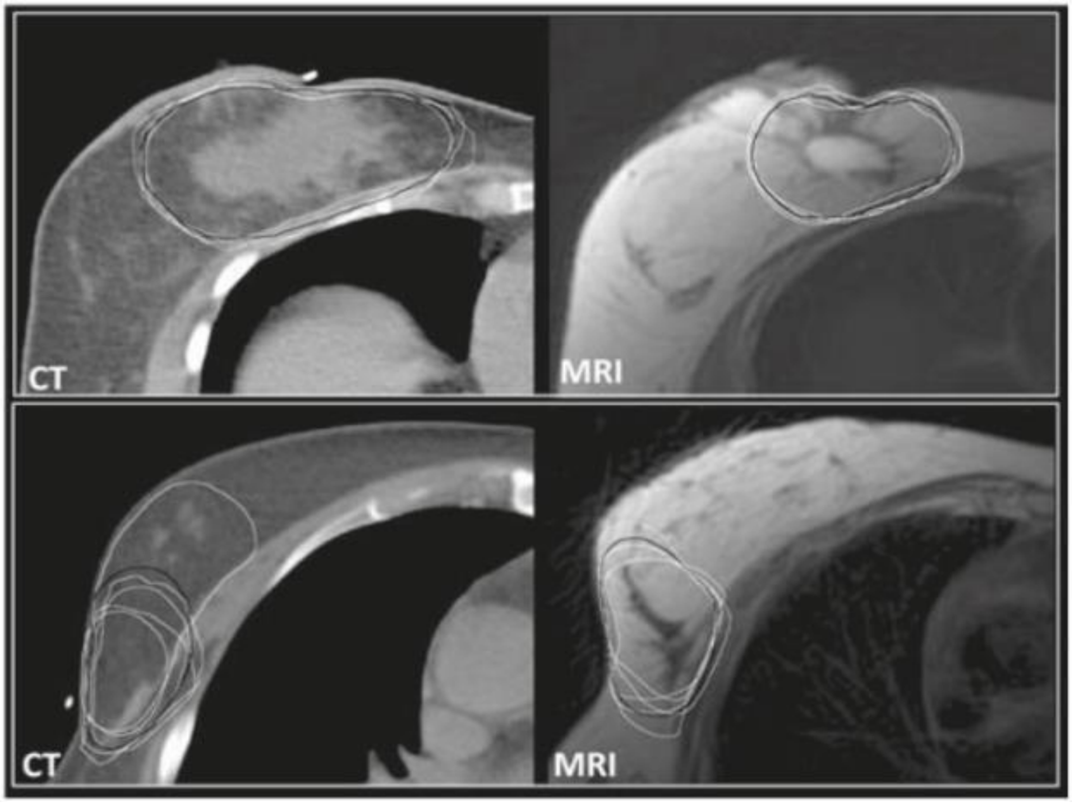
Said toxicity remains acceptable when proposing a hypofractionated treatment after boosting [34 - 37].

We found evidence that the use of simultaneous boosting integrated into hypofractionated breast treatment maintains local control rates and does not report significant changes at the cosmetic or symptomatic level, or acute toxicity [28-30 , 38-43].

Even when patients received systemic chemotherapy treatment, these rates of acute and chronic toxicity, as well as cosmetic results, remain acceptable [39].

The implementation of simultaneous boost with IMRT compared with 3D conformal radiotherapy increases compliance and decreases the dose to organs at risk [35].

Figure 5. Two examples of contouring based on tomography and resonance. It is observed how the interobserver variability is lower by using resonance.



Al-Hammadi N, et al. MRI reduces contour variation to increase clinical target volume in breast cancer patients without surgical clips in the tumor bed. Radiology and Oncology. 2017; 51(2): 160–168.

Superimpression (16 Gy in 8 fractions) with photons compared with electrons does not demonstrate a statistically significant difference in terms of acute, late toxicity, or cosmetic effects (at two years) [34].

When comparing the superimposition in a sequential or integrated way, it is evident that there is no difference in terms of the wet desquamation effect, finding a significant difference in favor of the integrated treatment in terms of grade 2 dermatitis and pruritus [36].

Figure 6. Template-based needle insertion and replacement with plastic catheters.

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Conclusions

Radiotherapy at the level of the tumor bed has been shown to improve local control rates. We did not find differences in the oncological results between the evaluated radiotherapeutic techniques . The delimitation of the tumor bed is a challenging task, the clips must be used as well as precise information of the surgical procedure. Institutions should evaluate the different international recommendations when defining their protocol regarding the indications for said treatment.

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Does not apply.

Administrative information

Abbreviations

ASTRO : American Society for Radiation Oncology.ESMO : European Society for Medical Oncology.
IG RT : Image Guided Radiation Therapy
IMRT : Intensity-modulated radiation therapy.
S IB : Simultaneous integrated boost

Additional Files

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Availability of data and materials

Data is available upon request to the corresponding author. No other materials are reported.

Author contributions

Santiago Roldán: Conceptualization, Formal analysis, Research, methodology, Project administration, Supervision, Validation, Visualization, Writing-original draft, Writing-revision and editing.
Karol Guzman: Conceptualization, formal analysis, research, validation, writing-revision and editing.
Marcelo Torres: Conceptualization, formal analysis, research, validation, writing-revision and editing.
Milexys Rivero: Supervision, validation, writing-revision and editing:
Leandro Ricagni: formal analysis, research, methodology, validation, visualization, writing -original draft.
Federico Lorenzo: Conceptualization, Formal analysis, Research, methodology, Project administration, Supervision, Validation, Visualization, Writing -original draft.
All authors read and approved the final version of the manuscript.

Ethics committee approval

It does not apply to observational studies and narrative reviews.

Consent for publication

The authors have the written authorization of the patient for the publication of images presented in this article.

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