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The 2024 Assisi think tank on breast cancer: Focus on the use of a tumour bed boost after breast conserving therapy

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ABSTRACT

At the Fifth Assisi Think Tank Meeting (ATTM) on breast cancer, one key topic was the role of tumor bed boost in invasive breast cancer and ductal carcinoma in situ. The need for a tumor bed boost after whole breast irradiation is controversial. A literature review assessed boost indications, target volume definition, techniques, dose fractionation, and ongoing trials. Findings indicated that while a boost halves the risk of local recurrence at 10 years, it also leads to worsened cosmetic outcomes and increased fibrosis without improving overall survival. Therefore, we would recommend to omit the boost if the estimated reduction in local recurrence at 10 years is less than 3 %, and to apply shared decision-making with patients, if the boost is expected to reduce the local recurrence

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rate with >3 % at 10 years. Future research will focus on identifying patient subgroups that can safely omit the boost and improving boost volume precision.

1. Introduction

Pivotal trials conducted in the 1980s and 1990s demonstrated the prognostic equivalence between mastectomy and breast conserving surgery (BCS) followed by radiotherapy (RT), aiming to achieve comparable overall survival (OS) [1–4]. Some trials that administered whole breast irradiation (WBI) included a boost dose to the tumour bed, while others did not [5–8]. When breast-conserving therapy (BCT), consisting of BCS followed by WBI, became the standard treatment for invasive breast cancer (BC), the question arose whether the standard 25 fractions (fx) of 2 Gy WBI needed to be supplemented with a tumour bed boost of 2 Gy x 5–8 fx. Several trials were performed to investigate this research question, where the largest was the EORTC boost versus no boost trial [9]. Results at 10 and 20 years showed that the 16 Gy boost reduced the local recurrence (LR) rate. Specifically at 20-year the hazard ratios (HRs) ranged from 0.56 for patients ≤40 years to 0.66 for patients >60 years and the LR reduced by almost 5 % (from 16.4 % without boost to 12 % with boost) in patients aged 50 years or younger [5,9]. Due to the higher LR rate in younger patients, the absolute benefit of the boost was also higher in this group. However, the boost did not improve the OS [5]. Since young patients are often affected by more aggressive BC biology and experience a not negligible rate of LR, the Young Boost Trial was conducted between 2004 and 2011; BC patients aged ≤50 years who were randomized to receive the standard boost dose of 16 Gy or (an equivalent of) 26 Gy to the tumour bed [10]. The 10-year results showed a slight benefit of the higher boost dose in terms of LR (4.2 vs 2.8 %) but at the cost of a significantly worse cosmetic outcome and more fibrosis [10]. In addition, again no improvement in OS was found by delivering a high-dose boost. Even in the low-dose boost arm, the 10-year local control rate was extremely high in these young BC patients (95.8 %). This improved local control which is currently seen in all contemporary trials [e.g. START, Fast Forward, DBCG], is probably due to a variety of factors, such as earlier diagnosis with smaller tumour stage, more accurate diagnostic imaging, better surgery, more detailed pathological evaluations, better RT and more effective systemic treatments [11–14]. These low LR rates, in combination with the awareness that a tumour bed boost does not improve the survival, but significantly impacts on cosmetic outcomes and increases fibrosis, have resulted in a wide variation in the application of the tumour bed boost. For example, in the DBCG Hypo trial only 15 % of the patients enrolled in Denmark, received a tumour bed boost, whilst the 85 % of those enrolled in Germany [12]. In the Netherlands, tumour bed boost administration varied between clinics and decreased over time. Indeed, the proportion of BC patients receiving a boost ranged from 37.3 to 92.7 % in 2011 to 28.3–65.4 % in 2016 [15].

Therefore, the application of a boost was selected by the steering committee as one of the 3 topics to be discussed in the “Assisi Think Tank Meeting” (ATTM) on BC in February 2024. The ATTM meeting was first organized in March 2016, in Assisi, Italy and has led to subsequent biannual 3-day “Think Tank Meetings” in 2018, 2020, 2022 and 2024 [16–19]. All were endorsed by the European Society for RadioTherapy & Oncology (ESTRO) and the Italian Association of Radiotherapy and Clinical Oncology (AIRO) and conducted under the auspices of the European Society of Breast Cancer Specialists (EUSOMA). These meetings aim to discuss in-depth current practice, to identify grey areas in the management of BC and RT, and to propose research directions to fill the gaps in evidence. Usually, three topics are selected by the steering committee prior to the meeting. Then, three working groups are composed to prepare the meeting. This preparation consists of reviewing the literature and ongoing trials for each topic. At the meeting, the results of the preparations are presented, potential approaches to address the identified challenges are discussed and research questions are defined. The meeting concluded with a concrete clinical study to fill the evidence gap. This manuscript reports on the topic of a tumour bed boost at the ATTM meeting in 2024.

2. Methods

The work is presented in three main sections:

1. Review of the literature: randomized clinical trials and systematic reviews published to date were selected from PubMed and reviewed to document the scientific evidence available to date. The following search terms were used: Invasive breast cancer, DCIS, boost, and locoregional recurrences.
2. Review of ongoing clinical trials: clinical.trials.gov was searched limiting trials to those with a known status and were not closed and recruiting patients at the present time. The following search terms were used: Breast Cancer, Radiotherapy, Tumour bed, Boost.
3. Proposal of a research direction on how to address the identified gap of evidence.

The first two parts were carried out before the meeting. During the meeting, the results were discussed, and a research question was identified. Subsequently, part 3 was addressed during the meeting in interactive working group-sessions.

3. Results

3.1. Review of the literature

3.1.1. Effect of a boost dose on local control and overall survival (OS)

More than 70 % (6%–95 %) of BC LR occur near the site of the resected primary tumour probably due to the persistence of microscopic tumour cells after surgery. The concept of a tumour bed boost arises from the fact that a higher dose of RT can possibly eliminate this subclinical tumour focus [20,21]. Recurrences in other quadrants of the breast are usually considered new primary tumours [1,12,22–28]. As true recurrence and new primary ipsilateral breast tumour have different natural histories and prognoses, this distinction has significant implications for therapeutic strategy [29].

Five randomized trials (the Lyon, Budapest, Australian-SGW, Nice and EORTC) including more than 8000 patients evaluated the role of a boost in invasive BC. All trials included patients with invasive BC, and the Australian-SGW trial also included patients with ductal carcinoma in situ (DCIS) [5,6,30–32]. In the Lyon and Nice trials, the boost dose was 10 Gy [6,32] and in the others it was 16 Gy. Boost was sequential to WBI and was delivered in conventional or hypofractionated schedules [33,34]. After a median follow-up ranging from 3 years in the Lyon trial to 17.2 years in the EORTC trial, the LR rate was decreased in those patients who received a boost dose to the tumour bed, except in the Nice trial which revealed no significant differences in terms of LR at a median follow-up of 6 years [5,6,32]. In the EORTC trial, which included 5318 early stage BC patients randomized to receive or not 8 fx of 2 Gy boost to the tumour bed after the 25 fx of 2 Gy WBI; the relative benefit in reducing local recurrence with the boost was approximately 50 % at 10 years and 35 % at 20 years [9]. The 20-year cumulative incidence of LR after complete excision of the tumour was 16.4 % in the no-boost group versus 12.0 % in the boost group ($p < 0{\cdot}0001$). However, moderate to severe fibrosis increased from 15.0 % to 30.4 % ($p < 0{\cdot}0001$). The absolute 20-year LR risk reduction decreased with increasing age: 11.6 % (36.0 % in the no-boost group *vs* 24·4 % after a boost) for patients ≤40

years; 5.9 % (19.4 % *vs* 13.5 %) for patients 41–50 years; 2.9 % (13.2 % *vs* 10.3 %) for patients 51–60 years; and 3.0 % (12·.% *vs* 9.7 %) for patients >60 years [9]. This results into the largest absolute benefit for patients with higher risk factors for LR, such as age below or equal to 40 years [5]. In the EORTC trial, 251 patients with a microscopically incomplete tumour excision were randomized to receive a boost of 10 Gy (low-dose boost) or 26 Gy (high-dose boost); brachytherapy was delivered more frequently in the high-dose boost arm (27.6 %) compared to the low-dose group (9.8 %) [35]. At 10 years, the LR rate was 17.5 % *vs* 10.8 % in the low and high-dose boost groups, respectively ($p > 0.1$) while the risk for moderate to severe fibrosis increased from 24.0 % to 54.3 % ($p < 0.0001$) [35]. The Young Boost Trial, conducted between 2004 and 2011, included 2421 T1-2N1 BC patients younger than 51 years old. This trial compared the standard dose of 16 Gy with the high dose of 26 Gy; the boost was delivered with electrons in 20 % of cases, photons in 75 % and other techniques in 5 % [7]. After a median follow-up of 11.7 years, 109 LRs occurred, 61 of which in the low-dose arm and 48 in the high-dose boost arm. The actuarial 10-years LR rates were 4.2 % for the low-dose arm and 2.8 % for the high-dose group ($p = 0.006$). Although the difference in LR rates was statistically significant, it was accompanied by a clinically relevant increase side effects in the high-dose arm, such as marked or moderate fibrosis (45 % *vs* 27 % in the high-dose and low-dose arms, respectively) [7].

In a systematic review of five randomized controlled trials involving a total of 8325 women, Kindts et al. reported a better local control for patients receiving a tumour bed boost compared to those who did not receive the boost (HR = 0.640, 95 % Confidence Interval (CI) from 0.55 to 0.75) [36]. Subgroup analysis yielded a HR of 0.65 in favour of tumour bed boost in women older than 40 years [36]. In the review by Kayali et al., seven studies were included, three of them were from the EORTC trial [5,6,9,30,37–39]. Of these, six studies (85.7 %) showed the boost significantly improved local control independently of age (HRs ranging between 0.34 and 0.73), with the largest absolute benefit in younger patients. Given that studies have shown no impact on OS with the tumour bed boost, and that overall LR rate has decreased impressively in the last decades, with nowadays usually a 10 years LR < 5 %, important grey areas emerge for final clinical decisions in routine practice [36,40].

The role of a radiation boost in patients with DCIS has been a controversial topic, mainly because the studies exploring its effectiveness are mostly retrospective. The available randomized trial that includes only DCIS is the multicentre *BIG 3–07/TROG 07.01 trial*, which randomized 1608 non-low risk DCIS patients (with at least one of the following characteristics: age below 50 years, symptomatic presentation, palpable tumour, tumour size equal or larger than 15 mm, multifocal disease, intermediate or high nuclear grade, central necrosis, comedo-histology or radical surgical margin of <10 mm) to receive or not a boost [8]. Patients were randomized to one of four arms: WBI 50 Gy in 25 fx with or without 10 Gy boost in 5 fx, or WBI 42.5 Gy with or without 10 Gy boost in 4 fx [8,31]. The 5-year free-from-LR rates were 92·7 % (95 % CI 90·6–94·4 %) in the no-boost group and 97·1 % (95·6–98·1 %) in the boost group (HR 0·47; 0·31–0·72; $p < 0·001$). However, the boost group had higher rates of grade 2 or higher breast pain (10 % [8–12 %] *vs* 14 % [12–17 %], $p = 0·003$) and induration (6 % [5–8%] *vs* 14 % [11–16 %], $p < 0·001$). In the Australian-SWG trial mentioned before, which also included patients with DCIS, with a median follow-up of 6.6 years, the boost decreased the LR rate from 7.3 % to 2.9 % ($p < 0.001$), again at the price of increased side effects [8,31].

3.1.2. *Indications for a tumour bed boost in DCIS and invasive BC patients between 50 and 70 years old*

In the case of invasive BC, the risk factors for LR are young age, involved margins, high tumour grade, lympho-vascular invasion and triple negative molecular subtype [41,42]. In the EORTC Boost Trial, at 20 years, the boost after WBI had no effect on long-term OS, but improved local control, with the largest absolute benefit in young patients, although it increases the risk of moderate to severe fibrosis with increasing age. The absolute benefit of local control decreased to 3 % in patients over 50 years [9,41]. The authors concluded that the boost can be avoided in most women older than 60 years [9].

The role of adjuvant systemic therapy, whilst contributing to the reduced LR risks, is not well substantiated, except for the impact of the use of trastuzumab on the effect of a boost in patients with HER2+ BC. In the HERA-trial, of the 1082 patients who were treated with BCT and adjuvant chemotherapy and trastuzumab, 441 patients (40.8 %) received a boost and 641 patients (59.2 %) did not. Patient groups had similar baseline characteristics in terms of age, nodal involvement, and tumour grade. At a median follow-up of 11 years, LR occurred in 7 % versus 9 % in the boost and no-boost groups, respectively ($p = 0.33$). Also, patients <40 years, with a higher LR risk had no significantly lower LR after a boost. Adjuvant trastuzumab combined with WBI is associated with a significant reduction in the risk of LR in HER2+ BC patients [43,44].

Patients with residual tumour after primary systemic therapy (PST) could potentially benefit from its administration, however, there are no studies investigating the role of the boost [45]. The EBCTCG metanalysis, including 4756 patients, demonstrated a higher risk of LR using PST compared with postoperative chemotherapy. However, these data should be interpreted with caution for several reasons, including the enrollment of patients who did not undergo surgery, the enrollment period between 1983 and 2002 with now-outdated options for systemic therapy and surgery, and with the learning curve of PST still in progress. These findings are cautionary regarding de-escalation of local treatments after PST and may suggest a possible role for additional RT including a boost [45,46]. No firm evidence-based conclusions on the need for a boost after obtaining a pathologic complete response with PST can be drawn. However, given that patients who achieve a complete pathological tumour response usually have an excellent prognosis, it is reasonable to consider omission of boost for these patients.

Studies evaluating the role of boost RT in patients with DCIS include the Australian-SGW trial, which also considered invasive BC, and the randomized BIG 3–07/TROG 07.01 trial. The latter included patients with non-low-risk DCIS and demonstrated a benefit in local control rates, albeit at the cost of increased toxicity. It is important to note that most patients did not receive endocrine therapy. The decision to use a boost should involve discussions about the trade-off between the benefits of local control and the risk of side effects. Future genetic expression profiling may aid in shared decision-making, although the economic aspects of genomic testing need to be considered.

3.1.3. *Recommendations for target volume definition*

Many studies have shown that there is considerable inter-observer variation when delineating the target volume for the boost [47,48]. Similarly, it is known that a large boost volume results in significantly worse cosmesis [7,49]. Therefore, it is of utmost importance the boost volume is as accurately defined as possible and its size minimised. For the definition of the target volume, it is important to use all available information, including surgical clips, preoperative clinical findings and imaging studies (mammography, ultrasound, magnetic resonance imaging (MRI)), surgical and pathological reports, as well as the vision of the surgeon and the pathologist to meticulously reconstruct the position of the removed tumour, i.e. the primary tumour bed. Boersma et al. and the GEC-ESTRO have provided guidelines on how to define the tumour bed, and subsequently on the clinical target volume (CTV) [50,51]. In the Young Boost trial, the margin around the tumour bed, to generate the CTV, was 15 mm minus the tumour-free margin, resulting in large irradiated boost volumes (Volume receiving >95 % of the boost dose) with a median value around 130 cc, but varying up to 1308 cc [7]. In the IMPORT HIGH Trial, the tumour bed was clip-defined and any associated surgical change. Given the known risks of increased fibrosis with large boost volumes, no additional CTV margin was included for the IMPORT High boost volumes (photons used for all patients), resulting in

a median value of 13 cc. It was important to avoid irradiating the chest wall, the pectoral muscles and the skin, which was done by cropping the generated CTV within the CTV_Breast. Finally, the planning target volume (PTV) was created by adding a margin to the CTV, according to the centre's positioning and treatment verification protocol, varying from 4 mm to 10 mm [52,53].

Delineating the treatment volume for the boost is more difficult if oncoplastic surgery has been performed and can become a real challenge. Oncoplastic breast surgery with volume replacement results in larger resection specimens, as well as larger RT boost volumes, potentially harming the long-term aesthetic outcome. However, more research is needed to verify this possible negative influence of oncoplastic surgery on cosmetic outcomes and patients' quality of life, as most studies lack detailed information on the planning of tumour bed boost RT, and the evidence on long-term outcomes is limited. Existing recommendations for patient selection and careful multidisciplinary discussion on the pros and cons of interventions are crucial. Close cooperation between surgeons and clinical/radiation oncologists is essential during the planning of RT for the most complex oncoplastic surgery cases and could improve treatment quality [54,55].

3.1.4. Boost technique and dose fractionation

In the EORTC Boost Trial, 63 % of patients were treated with electrons, 28 % with photons, and 9 % with interstitial brachytherapy. No significant differences were seen in outcomes, while the median boost volume was 60 cc for brachytherapy, 144 cc for electrons and 288 cc for photons [56].

Concerning dose-fractionation, older trials prescribed 5–8 fx of 2 Gy each to a total dose of 10–16 Gy. In 2004, the Young Boost Trial was the first to introduce the simultaneous integrated boost (SIB) technique as an option [7]. Traditionally, the standard scheme was 25 fx of 2 Gy WBI followed by 8 fx of 2Gy boost. With the introduction of SIB, this changed to 28 fx of 1.81 Gy to the breast plus 0.49 Gy extra to the boost. The later national Dutch protocol for the SIB became 21 fx of 2.17 Gy to the breast plus 0.49 Gy to the boost; this resulted in similar oncological outcome as the sequential boost [57]. The IMPORT HIGH trial with 2617 patients, compared a standard sequential boost with two dose levels of a SIB [11]. After a median follow-up of 6.2 years, no differences in LR were observed, and toxicity outcomes were similar or lower in the SIB group compared to the control group [11]. As a result, a SIB of 36–40-48 Gy in 15 fx, equating 3.2 Gy/fx to the boost area was established as the standard in the IMPORT HIGH trial [11]. The trial supports the SIB technique, with intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT).

The future directions include defining which patients will have a clinically relevant benefit from a boost, integrating knowledge about patient-, tumour- and treatment-related factors, completed by information from genetics, multi-omics, metabolomics, radiomics, and artificial intelligence. Promising novel biomarkers to predict the response and toxicity to RT are being investigated [58]. Gene expression profiling tests such as the genomic-adjusted radiation dose (GARD) concept, the adjuvant RT intensification classifier (ARTIC), and the profile for the omission of adjuvant RT (POLAR) may help in the process of shared decisions with patients [58–60].

3.2. Current research studies

The search took place through the database of Clinicaltrials.gov. Finally, 11 ongoing clinical trials were included (Table 1). Eight out of the eleven studies investigate the boost in the post-operative setting, 2 for DCIS and 6 for invasive BC. The vast majority of the trials i.e. the first five trials in Table 1, investigate the effect of different fractionation schemes on toxicity. The other 3 trials in the post-operative setting focus on the effect of a boost on local control: one randomised trial in DCIS patients (Bonbis trial), and one prospective cohort study in HER2 positive patients (BOOST-HER2 trial); the third trial randomizes patients between two hypofractionation schemes for the boost (HYPART study), to investigate the effect on local control. The last three trials use Intraoperative RT or pre-operative RT to apply a tumour bed boost in patients either to enhance the pCR rate (IBISCO trial), or in the setting of oncoplastic BCS, with as primary endpoint toxicity.

3.3. Proposed research strategies

Based on the above-mentioned findings, we defined two important research questions: 1) In which patients does the benefit of the tumour bed boost outweigh the side effects? and 2) How to improve the accuracy of the tumour bed delineation, keeping it as small as possible? We focussed on the first research question since we considered that resolving this issue would have the largest positive impact on the outcome of patients and our clinical practices, especially since currently a wide practice variation is observed [61]. There are several main reasons for these practice variations. Firstly, surgical techniques and approaches have progressed and de-escalated compared to the previous historical phase 3 trials [62]. The removal of the primary tumour was performed with a margin, either with or without primary closure, and oncoplastic surgeries are also an option to remodel the breast [54]. Besides modern pathological evaluation, the guidelines for surgical margins have changed from wider margins to negative margins defined as "no tumour on ink" [63]. With all those advances listed above, the use and volume definition has been challenging and more complicated.

The first research question cannot be answered universally, since a shared decision regarding a boost must always take into account the patient's personal preferences and circumstances. To make an informed decision regarding a boost treatment, patients should receive comprehensive and robust information on risks and benefits based on high-quality data. Therefore, we decided to focus research on identifying groups in whom the boost may be omitted as risks may begin to outweigh benefits for most BC patients. As a starting point, we made two assumptions: 1) a 10–16 Gy boost to the tumour bed reduces the LR rate approximately with a factor of 2 at 10 years; 2) a reduction in LR rate <3 % at 10 years from the boost is not clinically relevant due to the increased risk of side effects and the fact that it does not improve the OS. The consequence of these assumptions is that a 10-year LR rate of <6 % without a boost is likely to be acceptable to patients in the context of a doubling of the risk of fibrosis with a boost. Therefore, the aim of the research is to define subgroups of patients with BC where a boost may safely be omitted. The study will consist of two phases.

In phase 1, data analysis will be run on existing study cohorts of patients treated with contemporary treatments (Table 2), to identify risk factors on LR with and without a boost treatment [12,64–67]. Univariate and multivariate analyses on each dataset separately, focusing on gain from a boost will be run to analyse the impact of established risk factors such as age, tumour size, grade, molecular subtype, surgical margins, and others known from literature. A multivariable logistic regression analysis across all datasets will be conducted to identify the combined effect of multiple risk factors on LR rates. Findings from the multivariable analyses will be used to define subgroups based on the combination of risk factors that predict a LR rate of less than 6 % at 10 years without a boost. This hypothesis will subsequently be tested and validated in an emulated trial across included cohorts.

In phase 2, if the hypothesis of phase 1 is confirmed, a prospective cohort study will be started, to further investigate whether omitting a boost to the tumour bed in the identified low-risk groups, indeed results in a 10-year LR < 6 %, or a 5-year LR < 3 % with current treatments.

Besides clinical research studies, uniform essential information collection for the use of boost treatment was advised to be reported in concordance to the ESTRO report or the PRECEDENT project in all prospective or retrospective studies [68,69].

Table 1
Ongoing clinical trials for Boost in invasive breast cancer (BC) and Ductal Carcinoma In Situ (DCIS) patients.

Trial	Principal Investigator Country Accrual Time	Population and study Summary	Number of Patients required Phase	Primary Endpoint	Fx scheme	Setting
NCT00907868 (BONBIS)	David Azria Institut du Cancer de Montpellier - Val d'Aurelle. France 2009–2023	Women with DCIS treated with BCS followed by WBI with or without RT to the tumour bed boost	2004 participants Phase III	Estimate and compare LR-free survival	25 fx of 2Gy±8 fx of 2Gy	Postoperative DCIS
NCT02958033	Min Xu Shandong Cancer Hospital Affiliated to Shandong University. Jinan, Shandong, China 2016–2019	Women with early BC treated with BCS randomized to accelerated hypo-fractioned WBI with a concurrent boost to the tumour bed vs conventional fractioned WBI with a concurrent boost to the tumour bed.	100 participants Phase III	Grade of acute skin toxicity (2 Weeks after the end of RT). Late toxicity (breast fibrosis and cardiac disease), cosmetic outcome, local control and survival	18 fx (2.5Gy WBI + SIB 2.88Gy) vs 28 fx (1.8Gy WBI + SIB 2.15Gy)	Postoperative Invasive BC
NCT05893966 (BOOST-HER2)	Haeyoung Kim Samsung Medical Center. Seoul, Republic of Korea 2022–2025	Prospective Cohort for Tumour Bed Boost RT in HER2+ BC after BCS	400 participants Cohorts	Ipsilateral breast tumour recurrence (7 years from the start of the RT)	N/A	Postoperative HER2+ Invasive BC
NCT04913532	Wenjie Ni Beijing Shijitan Hospital, Capital Medical University. Beijing, China 2021–2023	Women with early BC treated with BCS with Hypofractionation with SIB	40 participants Phase II	Acute Toxicity (6 months)	15 fx of 2.7Gy with SIB 15 of 3.2Gy	Postoperative Invasive BC
NCT04175210 (PRART)	Silvia Formenti Weill Medical College of Cornell University. New York, United States 2019–2024	Women with DCIS with BCS will be randomized to receive WBI with a concomitant boost to the tumour bed over 15 fx (Arm 1, standard) versus 10 fx (Arm 2, experimental)	400 participants Phase III	Adverse events between the two arms (up to 5 years)	15 fx of 2,7Gy with SIB 3.2 Gy vs 10 fx of 3.2Gy with SIB 4.2Gy	Postoperative DCIS
NCT04472845 (HYPART)	Budhi S Yadav Post Graduate Institute of Medical Education and Research. Chandigarh, India 2021–2023	HYPofractionated Adjuvant RadioTherapy in 1 Versus 2 Weeks in High-risk Patients With BC	1018 participants Phase III	Loco-regional recurrence (5, 10 and 15 years)	5 fx of 5.2Gy + 8 of 2Gy or SIB to 34Gy vs 10 fx of 3.4Gy + 8 of 2Gy or SIB to 42Gy	Postoperative Invasive BC
NCT03121248 (HAI-5-III)	Liv Veldeman Ghent University Hospital, Dept. Radiotherapy-Oncology. Ghent, Belgium 2017–2023	Women Over 65 Years for early and advanced BC after BCS	144 participants Phase III	Breast retraction (LENTSOMA) (2–5 years)	5 fx of 5.7Gy (SIB 6.2Gy) vs 15 fx of 2,67Gy (SIB 3.12Gy)	Postoperative Invasive BC
NCT03562273 (GCC1876)	Elizabeth M. Nichols University of Maryland. Baltimore, United States 2018–2023	Single-fx Boost Using a Breast Specific Radiosurgery Device, The GammaPodTM Registry Study and Evaluation of QoL	160 participants Cohorts	QoL evaluations (1 year)	1 fx of 8 Gy with gammapod prior to WBI	Postoperative Invasive BC and DCIS
NCT05673304 (IBISCO)	Alessio G Morganti IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy 2024–2026	Luminal B BC patients After Preoperative With SBRT and NACT	30 participants Phase II	pCR (6 month after SBRT at surgery)	SBRT	Preoperative NACT
NCT02927912	Jose Bazan Ohio State University Comprehensive Cancer Center. Ohio, United States 2017–2023	IOERT Boost at the Time of BCS With Oncoplastic Reconstruction in Women With early BC	176 participants Phase II	Rate of grade 3 breast fibrosis (1 year)	IOERT boost followed by WBI	Intraoperative Invasive BC
NCT05603078 (BIRKIN)	Hao Jing Cancer Institute and Hospital, Chinese Academy of Medical Sciences. Beijing, China 2022–2026	Preoperative MRI Linac-based Tumour-bed Boost (single fx) Followed by Breast-conservative Oncoplastic Surgery and Adjuvant Ultra-hypofractionated WBI for Early BC	102 participants Phase II	Acute toxicities (4 weeks after RT)	Preoperative 1 fx of 10Gy + WBI 5 fx of 5.2Gy	Preoperative

BC: Breast Cancer; DCIS: Ductal carcinoma In Situ; Fx: fractions; BCS: Breast Conserving Surgery; WBI: Whole Breast Irradiation; RT: Radiotherapy; NACT: Neoadjuvant Chemotherapy; SIB: Simultaneous Integrated Boost; QoL: Quality of Life; IOERT: Intraoperative Electron Radiotherapy; pCR: pathological complete response; SBRT: Stereotactic Radiation Therapy; *MRI: Magnetic Resonance Imaging; NA: Not available.*

Table 2
Study cohorts selected to investigate the variables related to local control.

Trial/Study	Period	Number of patients Mean age	% with and without boost
NCT01993498 Canto-RT (France) [64,70] Prospective clinical cohort study including patients with stage I-III BC from 26 French cancer centers	2012–2018	12,012, where 73.1 % had BCT 56.6	Among BCT for whom RT data were collected: 68.6 % 31.4 %
NCT00909818 Danish Breast Cancer Group (DBCG) HYPO Hypofractionated Versus Standard Fractionated RT in Patients With Early BC or DCIS in a Randomized Phase III	2009–2014	1854 59	15 % 85 %
DBCG IMN2 Study [65], 50 % of patients had BCT	2007–2014	4200 59	23.1 % 76.9 %
NCT02384733 DBCG Skagen trial 1 [71] Moderately hypofractionated loco-regional adjuvant radiation therapy of early breast cancer combined with a simultaneous integrated boost in patients with an indication for boost: DBCG HYPO II, a randomized clinically controlled trial	2015–2021	2879 pts, where 52 % had BCT 57	Among BCT: 18 % had boost, all SIB
NCT03127995 HypoG-01 [72] Hypofractionated Versus Standard Fractionated RT in Patients With Early BC with an indication of locoregional irradiation in a Randomized, controlled, Phase III trial	2016–2020	1265 pts, where 54.4 % had BCT 58	Among BCT: 48.5 % had boost among them 32.2 % SIB and 67.8 sequential boost 51.5 %
Dutch Cancer Registry (DCR) (NL) [67]	2012–2016	About 35,000 patients 62	55 % 45 %
EORTC 22922/10,925 [73]	1996–2004	4004 54	85.2 % 14.8 %

BC: Breast Cancer; DCIS: Ductal carcinoma In Situ; Fx: fractions; WBI: Whole Breast Irradiation; RT: Radiation Therapy; NA: Not available; BCT: Breast conserving treatment; SIB: Simultaneous integrated boost.

4. Conclusions

In summary, although a tumour bed boost seems to reduce the LR rate by nearly half, the LR rate without a boost is already so low in most patients that the benefits do not outweigh the associated side effects. Up till now there is no consensus on how to select patients in whom the benefit of a tumour bed boost outweighs the side-effects. The same applies to a tumour bed boost after BCS for DCIS. Since the 10-year LR risk has reduced considerably in the last 1-2 decades, and since a boost dose to the tumour bed does not improve overall survival, we recommend that the delivery of a boost should be part of the shared decision-making with the patient if the estimated reduction in LR $>$ 3 %. The highest risk patients for LR were listed as young age, large tumour, no response to PST, involved margins, high tumour grade, lympho-vascular invasion, extensive intraductal component and triple negative molecular subtype. To further refine this, we encourage to aim further research at identifying patients in whom a boost can safely be omitted, i.e. with an estimated absolute reduction in LR of $\leq$3 %. It is important to keep in mind that breast surgery and RT techniques have improved since the trials that studied the role of the boost. These advances will likely lead to better cosmetic outcomes and quality of life.

CRediT authorship contribution statement

Meritxell Arenas: Writing – review & editing, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yasemin Bölükbaşı:** Writing – review & editing, Validation, Methodology, Data curation, Conceptualization. **Liesbeth J. Boersma:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Birgitte Offersen:** Writing – review & editing, Validation, Methodology, Conceptualization. **Vassilis Kouloulias:** Writing – review & editing. **Isabella Palumbo:** Writing – review & editing. **Lurdes Trigo:** Writing – review & editing. **Laura Lozza:** Writing – review & editing. **Fabio Marazzi:** Writing – review & editing. **Marco Trovo:** Writing – review & editing. **Sofia Rivera:** Writing – review & editing. **Orit Kaidar-Person:** Writing – review & editing. **Charlotte Coles:** Writing – review & editing. **Icro Meattini:** Writing – review & editing. **Vincenzo Valentini:** Writing – review & editing. **Cynthia Aristei:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Philip Poortmans:** Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization.

Ethical approval

Ethical approval was not required.

Declaration of competing interests

All the authors declare no confict of interest.

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