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Tumor Bed Boost Integration during Whole Breast Radiotherapy: A Review of the Current Evidence

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Summary

Radiation therapy delivered with hypofractionation, which involves the delivery of a higher dose per fraction in fewer fractions (generally with a lower total nominal dose) over a shorter overall treatment time, is an established therapeutic option at least for a selected group of early breast cancer patients after breast-conserving surgery. Optimal delivery of the tumor bed boost dose in terms of timing, fractionation, and total dose whenever a hypofractionated schedule is employed has yet to be established. We herein present a review of the current evidence on the role of boost integration in whole breast radiotherapy.

Introduction

Combining breast-conserving surgery (BCS) and radiation therapy (RT) is a mainstay option in the multimodality treatment of breast cancer with optimal long-term local control, mild toxicity, good cosmetic outcome, and survival rates comparable to mastectomy [1]. Adjuvant whole breast radiotherapy (WBRT) yields a local failure rate of 3–15% depending on the patient cohort and variables such as intrinsic risk factors, type of surgery, and follow-up time [2]. However, in recent years, substantial improvements in the fields of early diagnosis, clinical selection, surgery, RT technology, and systemic treatments have led to an increase in local control, with higher rates than those observed in early randomized trials [3]. It has been demonstrated that good local control translates into improved overall survival (OS) [4]. The rationale for delivering an adjunctive radiation dose boosting the lumpectomy cavity is derived from several considerations: First, the radiobiological observation of a dose-response relationship for breast cancer; second, the pathological evidence of a higher microscopic tumor burden in proximity to the site of lumpectomy; and third, the clinical observation of the local pattern of failure close to the primary tumor location [5–7]. Randomized phase III trials exploring the role of boosting the tumor bed demonstrated a relative reduction in local failure in the range of 20–50%, depending on risk factors of the patient cluster analyzed [2]. However, in spite of this substantial clinical benefit, in several countries there has been a tendency to omit adjuvant WBRT after BCS, especially in women over 70–80 years, but also in younger patients, maybe due to the extended overall treatment time using a conventionally fractionated schedule and sequential boost approach [8]. Hypofractionation (HF) (delivery of a larger dose per fraction in shorter overall time) and concurrent boost (delivery of a synchronous adjunctive dose to the tumor bed) represent a useful option to optimize treatment both for patients and healthcare providers [9].

Boosting the Tumor Bed

Local Control and Cosmetic Outcome

A boost dose to the lumpectomy cavity can be delivered with external photon beam RT, external electron beam RT, and high-dose brachytherapy employing an after-loading system administered either intraoperatively or after WBRT. Boosting the tumor

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bed in addition to WBRT has been shown to improve local control with mild side effects and acceptable cosmetic outcome in several randomized phase III trials. The absolute gain ranges from 1 to 40%, while the relative local failure reduction varies from 20 to 50% depending on the characteristics of the cohort [2]. The EORTC 'Boost Versus No Boost' trial (22881/10882) randomized 5,318 patients (after clear-margin BCS) to receive conventionally fractionated WBRT (50 Gy/25 fractions (fr)) with either an additional 16 Gy/8 fr boost (or 15 Gy low-dose rate brachytherapy) or not [10]. The boost dose provided a benefit in terms of local failure (6.2 vs. 10.2% at 10 years; $p < 0.0001$), predominantly in younger patients (< 40 years), with a hazard ratio of local recurrence of 0.59 [11]. However, the 16 Gy boost group had worse cosmetic results (photographic assessment with a subjective panel and objective measurements) than the no boost group, in terms of 10-year severe fibrosis (4.4 vs. 1.6%) [11]. In the Lyon trial, 1,024 T1–T2 breast cancer patients were randomized to receive a hypofractionated (50 Gy; 2.5 Gy daily) WBRT schedule (50 Gy/20 fr; 2.5 Gy/daily) with either an additional 10 Gy hypofractionated sequential boost (10 Gy/4 fr; 2.5 Gy daily) or no boost [12]. The boost dose resulted in a lower local recurrence rate (3.6 vs. 4.5%; $p < 0.05$) and a higher rate of G1–G2 telangiectasia (12.4 vs. 5.9%) but no difference in cosmetic self-scoring and scoring results obtained by the physician [12]. The Budapest trial, reporting on 207 patients (1/3 of the planned study group of 604 patients), compared a boost strategy (16 Gy/8 fr with electrons or 12–14.25 Gy with high-dose rate brachytherapy) after conventionally fractionated WBRT (50 Gy/25 fr) [13]. Boost dose improved local control (local failure 7.3 vs. 15.1%), especially in younger patients with positive surgical margins and a high proliferation index. A non-significant decrease in physician-based cosmetic results was observed in the boost arm and a higher rate of fat necrosis [13]. The St. George and Wollongong (SGW) trial randomized 688 breast cancer patients to receive conventionally fractionated WBRT (50 Gy/25 fr) with no boost vs. lower dose WBRT (45 Gy/25 fr) and a sequential boost of 16 Gy/8 fr delivered with electrons [14]. In the 6-year analysis, no difference in terms of local control could be detected between treatment arms [15]. Nevertheless, the boost arm had improved overall cosmetic results as assessed by an external expert panel (79 vs. 68%; $p = 0.016$) and a lower (not statistically significant) breast retraction assessment score, maybe due to the reduced whole-breast dose [14]. However, generally, the application of a tumor bed boost dose is recommended for patients below the age of 40 having a large tumor, close surgical margins, high-grade invasive or in situ ductal tumors, a high proliferation index, hormone receptor-negative tumors, and an extensive intraductal component [2].

How to Fit with Hypofractionation

The administration of daily doses higher than 1.8–2 Gy using HF is a common option for WBRT after BCS for early breast cancer [16]. HF has been used in several institutions for decades and tested in randomized controlled trials (RCTs) [17]. In the United Kingdom, comprehensive guidelines by the National Institute of Clinical Excellence (NICE) on the management of early breast cancer recommend HF (40 Gy/15 fr) as the standard solution [18]. Potential advantages of HF are directed at patients (convenience and costs), radiotherapy departments (patients turnover), and global health systems (costs) [9]. The American Society for Radiation Oncology (ASTRO) recommends the use of HF to deliver WBRT for patients with the following features: early breast cancer, age ≥ 50 years, stage pT1–pT2, dose homogeneity within ± 7% in the central axis plane of the treatment plan, and being chemotherapy-naïve [19]. 4 large phase III RCTs investigated the role of HF versus conventional fractionation (50 Gy/25 fr over 5 weeks) in terms of local recurrence rate, side effects, and cosmetic results. The RMH/GOC trial randomized 1,410 patients with T1–T3/N0–N1 (after clear-margins BCS) to 3 different WBRT schedules delivered over 5 weeks: conventional fractionation vs. 39 Gy/13 fr (3 Gy daily) and 42.9 Gy/13 fr (3.3 Gy/day). In this study, 75 % of patients received a direct electron field boost dose to the tumor bed (14 Gy/7 fr) [20]. The multi-institutional START A trial enrolled 2,236 women with a trial design similar to RMH/GOC except for a decreased daily dose (3.2–41.6 Gy/13 fr) in the second experimental arm. In this study, 60.6% of patients received an extra dose to the tumor bed [21]. The START B trial accrued 2,215 patients with the same eligibility criteria as START A. The experimental arm accelerated treatment with 40 Gy/15 fr over 3 weeks. Only 42.6 % of patients received a boost dose [22]. Finally, the Canadian trial, updated with a median follow-up of 10 years, randomized T1–T2 node-negative breast cancer patients with negative margins to receive 42.5 Gy/16 fr over 3.5 weeks or standard fractionation, without any boost dose [23]. None of the 4 RCTs explored the use of the boost dose to the tumor bed within their treatment protocol. The Canadian trial had no boost. The UK trials delivered a conventionally fractionated boost dose sequential to WBRT, at the institution's discretion, with a 1–2-week increase in overall treatment time. Thus, no definitive conclusions may be drawn from these trials about the ideal integration of tumor bed boost and WBRT whenever HF is employed. Table 1 shows an overview of clinical data on HF trials.

Why Integration with WBRT Might Work

At present, the optimal hypofractionted WBRT regimen to be delivered whenever a boost to the tumor bed is planned has not yet been determined; neither has the optimal tumor bed boost dose and fractionation to be adopted in conjunction with WBRT schedules employing HF. Finally, the timing of the combination, concomitant or sequential, has yet to be established. The incorporation of the boost dose within WBRT, with concurrent delivery, concomitant boost, or simultaneous integrated boost (SIB) increases the time-saving benefit of HF in the WBRT phase, further reducing overall treatment time. Moreover, the incorporation of the boost within the whole breast phase provides a dosimetric advantage towards both organs at risk and target volumes. Several dosimetric

Table 1. Phase III trials investigating hypofractionated whole breast radiotherapy in breast cancer

Study [ref.]	Country	Patients, n	Dose/ fractionation	Patients receiving boost dose, %	Median observation time, years	Local relapse rate, %
OCOG [23]	Canada	612	50 Gy/25 fr (2 Gy daily)	0	10	6.7
		622	42.5 Gy/16 fr (2.65 Gy daily)	0		6.2
RMH/GOC [48]	UK	470	50 Gy/25 fr (2 Gy daily)	74	10	12.1
		466	42.9 Gy/13 fr (3.3 Gy daily)	75		9.6
		474	39 Gy/13 fr (3 Gy daily)	74		14.4
START A [21]	UK	749	50 Gy/25 fr (2 Gy daily)	60	5	3.6
		750	41.6 Gy/13 fr (3.2 Gy daily)	61		3.5
		737	39 Gy/13 fr (3 Gy daily)	61		5.2
START B [22]	UK	1,105	50 Gy/25 fr (2 Gy daily)	41	10	5.5
		1,110	40.05 Gy/15 fr (2.67 Gy daily)	44		4.3

fr = Fractions.

comparison planning studies investigated the potential advantage of boost integration. Singla et al. [24] compared SIB plans using intensity-modulated radiation therapy (IMRT) vs. 3D conformal RT to deliver a 16 Gy tumor bed SIB above 50.4 Gy of conventionally fractionated WBRT. An improvement in target conformity (up to 67%) could be detected with IMRT SIB as a reduction in mean lung dose (MLD) and maximum heart dose. Hurkmans et al. [25] performed a planning study of SIB using inverse optimization vs. a 3-field boost approach. The comparison demonstrated similar volume of whole breast and tumor bed receiving > 95% of the prescribed dose and a similar mean heart dose (MHD) and MLD. Interestingly, the SIB approach provided better conformity and a reduction in the volume of whole breast (excluding the boost volume) receiving > 95% of the prescribed dose. This is in line with other findings. Van der Laan et al. [26] reported on a comparative planning study of SIB in 30 patients affected by left-sided breast cancer, comparing standard RT (50 Gy/25 fr + 16 Gy/8 fr) as a sequential boost vs. a forward-planned 3D conformal WBRT delivering 1.81 Gy × 28 fr with a concomitant boost of 0.49 Gy (2.3 daily). With boost incorporation, the mean volume of whole breast getting ≥ 107% of the prescribed dose was reduced by 20%, the mean volume of breast tissue outside the tumor bed receiving ≥ 95% of the boost dose was reduced by 54%, and MHD and MLD were reduced by 10%. Consistently, in a comparison between 3D conformal RT and helical tomotherapy for WBRT, Hijal et al. [27] demonstrated that a tomotherapy-based SIB approach leads to a reduction in excess irradiation of the whole breast excluding the tumor bed. With the 3D conformal technique, a large amount of breast tissue outside the tumor bed was untimely irradiated. This issue has clinical implications. Interestingly, Franco et al. [28], using static ports of tomotherapy for conventionally fractionated WBRT (50 Gy/25 fr) and a sequential boost (10–16 Gy/5–8 fr) delivered with helical tomotherapy, demonstrated that the adjunctive dose received by the whole breast volume minus the tumor bed volume ($V_{52,5Gy}$, V_{55Gy}, $V_{57.5Gy}$) was correlated with G2–G3 acute skin toxicity [28]. In that cohort of 120 patients, more than 1/3 of the whole breast received 105% of the prescribed dose, almost 1/5 received 110%, and more than 1/10 received 115%, due to the sequential boost phase. In a subsequent phase II trial, Franco et al. [29] employed a static angle tomotherapy approach to deliver hypofractionated SIB WBRT achieving consistent dosimetric results as $V_{105\%}$ (for whole breast planning target volume (PTV) minus tumor bed PTV) was very low (2.4 ± 0.9) and $V_{110\%}$ negligible (0.01), strongly limiting unintended irradiation outside the tumor bed. These dosimetric results were reflected by a robust reduction in acute skin toxicity. Figure 1 shows beam arrangements, dose distributions, and consequent dose-volume histograms of right-sided (fig. 1a) and left-sided (fig. 1b) breast cancer treated with hypofractionated WBRT, employing a SIB approach to the tumor bed delivered with static ports of tomotherapy.

Clinical Data on Concurrent Boost

Several mono-institutional prospective or retrospective studies provided clinical data on boost integration during WBRT. Recently, a German multicenter study (ARO-2010–01) reported the feasibility and adherence to dose constraints of a SIB schedule in early breast cancer patients after BCS (40 Gy/16 fr, 2.5 Gy daily as WBRT; 48 Gy/16 fr, 3 Gy/16 fr to the tumor bed) [30]. Freedman et

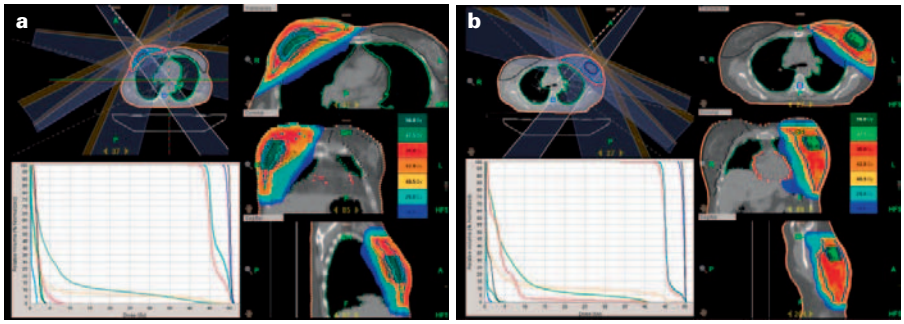

Fig. 1. Examples of hypofractionation and simultaneous integrated boost (SIB) delivered with static ports of tomotherapy (**a** right- and **b** left-sided breast cancer).

al. [31] (Fox Chase Cancer Center) enrolled 75 patients (Tis–T2 breast cancer with clear resection margins) into a phase II trial of photon-based WBRT delivered over 4 weeks up to 45 Gy/20 fr (2.25 Gy daily) with an IMRT incorporated boost of 2.8 Gy daily to 56 Gy/20 fr. 5-year local control was 97.3%. Cosmetic outcome, evaluated using a patient- and physician-reported Breast Cancer Treatment Outcome Scale (BCTOS), was close to excellent with minimal difference between treated and untreated breasts. Chadha et al. [32] (Beth Israel Medical Center) treated 160 early breast cancer patients (Tis–T2, node-negative, negative resection margins, and chemotherapy-naïve) with accelerated HF RT delivering 40.5 Gy/15 fr (2.7 Gy daily) to the whole breast (over 3 weeks; 19 days) with an adjunctive concurrent 0.3 Gy daily to the tumor bed, to 45 Gy/15 fr. With a median follow-up of 3.5 years, the 5-year OS and disease-free survival (DFS) were 90 and 97%, respectively; local control was 99%. No late toxicity higher than G2 according to the LENT-SOMA scale was observed among patients with > 2 years follow-up. Formenti et al. [33] (NYU) enrolled 91 women into a single-arm prospective study of WBRT in prone position to 40.5 Gy/15 fr (2.7 Gy daily) over 3 weeks. A SIB was delivered to the tumor bed with IMRT to receive 45 Gy/15 fr (3 Gy daily; adjunctive 0.3 Gy daily). With a median follow-up of 12 months, 1 recurrence, 2 acute grade 3 toxicities according to RTOG/EORTC (reversible grade 1–2 dermatitis in 67% of patients), and no grade 3 late effects according to LENT-SOMA were observed (grade 1 fibrosis in 48% of patients; grade 2 in 3%). McDonald et al. [34] reported the 3-year outcome of a retrospective series of 354 patients (stage I–III disease, mostly free margins; node positivity allowed) treated with IMRT SIB consisting of 45 Gy/25 fr (1.8 Gy daily) to the whole breast and 2.14 Gy each day to the tumor bed concurrently, followed by a dedicated cavity boost of another 3 fr (2.14 Gy) to 59.92 Gy. Grade 3 acute toxicity was < 1%, 3-year locoregional recurrence was 2.8% (among invasive breast cancers), and global cosmetic outcome was good to excellent in 96.5%. Bantema-Joppe et al. [35] treated, between 2005 and 2010, 940 patients with standard fractionated WBRT (50.4 Gy/28 fr; 1.8 Gy daily) and a SIB regimen to the tumor bed (2.3–2.4 Gy daily up to 64.4–67.2 Gy). 3-year locoregional control, recurrence-free survival, and OS rates were 99.2, 95.5, and 97.1%, respectively. 5-year local control was 98.9% [36]. Regarding toxicity and cosmetic outcome, after a median follow-up time of 30 months (range 6–54 months), 8.5% of patients had ≥ G2 fibrosis in the boost area, chest wall pain was detected in 6.7%, and teleangiectasia was detected in 3.7% (≥ G2) [37]. Half of the patients developed all-grade fibrosis outside the tumor bed. Finally, Cante et al. [38, 39] reported data on HF and concomitant boost with a schedule consisting of 45 Gy/20 fr delivered to the whole breast (2.25 daily) and an adjunctive 0.25 Gy daily dose to the tumor bed to a total nominal dose of 50 Gy (2.5 Gy daily). The whole course was given over 4 weeks (26 days). After a median follow-up of 60 months, outcomes were consistent (OS 97.6%; cancer-specific survival 99.4%; DFS 96.6%; local control 100%). Cosmetic outcome was scored as excellent/good in 95.7% of patients. Selected mono-arm clinical series are presented in table 2.

Ongoing Trials with Boost Integration

Few prospective studies are presently investigating the role of boost integration during WBRT employing HF. The RTOG 1005 trial is a phase III prospective trial investigating accelerated WBRT for early breast cancer, comparing standard RT (50 Gy/25 fr) (with HF option of 42.7/16 fr; 2.67 Gy daily) followed by a sequential boost of 12–14 Gy/6–7 fr vs. a hypofractionated accelerated WBRT schedule of 40 Gy/15 fr (2.67 Gy daily) with a concomitant boost of 3.2 Gy to the tumor bed (up to 48 Gy/15 fr). This trial has been recently closed to accrual, and results are eagerly awaited [40]. The IMPORT High trial tests dose-escalated RT delivered with IMRT in early breast cancer patients with higher than average risk of local recurrence, with the primary endpoint of palpable induration inside the boost volume of the irradiated breast [41]. The standard arm comprises 40.5 Gy/15 fr (2.7 Gy daily) and a sequential tumor bed boost of 16 Gy/8 fr for an extra 1.6 weeks (23 fractions for total of 4.6 weeks). 2 different experimental arms were chosen: in addition to 2.4 Gy × 15 fr to the whole breast and 2.67 Gy × 15 fr to the index quadrant, the first arm receives 3.2 Gy × 15 fr (up to 48 Gy), while the second arm receives 3.53 Gy × 15 fr (up to 53 Gy) to the tumor bed. These schedules were calculated (considering an α/β ratio = 3 Gy for tumor control) as isoeffective to 60 Gy and 69 Gy, respectively. The global sample size is 2,568 patients: to date 61% have been accrued and the closure date is planned for next year (April 2015) [42]. The German IMRT-MC2 is a prospective, 2-armed (251 patients in each arm), multicenter, randomized phase III

Table 2. Selected clinical series testing hypofractionation and a concomitant tumor bed boost in breast cancer radiotherapy

Study [ref.]	Country	Patients, n	Whole breast fractionation	Boost fractionation	Observation time, years	In-breast failure rate, %
Corvo et al. [49]	Italy	377	46 Gy/20 fr (2.3 Gy daily)	1.2 Gy weekly over WBRT	3	0
Cante et al. [39]	Italy	375	45 Gy/20 fr (2.25 Gy daily)	50 Gy/20 fr (2.5 Gy daily)	5	0
Morganti et al. [50]	Italy	201	40 Gy/16 fr (2.5 Gy daily) 50 Gy/25 fr (2 Gy daily)	44 Gy/16 fr (2.75 Gy daily) 60 Gy/25 fr (2.4 Gy daily)	2.6	0
Formenti et al. [51]	USA	91	40.5 Gy/15 fr (2.7 Gy daily)	48 Gy/15 fr (3.2 Gy daily)	1	0
Freedman et al. [31]	USA	75	45 Gy/20 fr (2.25 Gy daily)	58 Gy/20 fr (2.8 Gy daily)	5.8	2.7

fr = Fractions; WBRT = whole breast radiotherapy.

Table 3. Prospective phase III trials testing hypofractionation and concomitant boost for breast cancer radiotherapy

Study [ref.]	Country	Primary endpoint	Target population, n	Dose and fractionation (experimental arm)		
				whole breast	index quadrant	tumor bed
RTOG 1005 [40]	USA	in-breast relapse	2,300	40.05 Gy/15 fr (2.67 Gy daily)	/	48 Gy/15 fr (3.2 Gy daily)
IMPORT-HIGH [42]	UK	palpable induration	2,568	36 Gy/15 fr (2.4 Gy daily)	40.05 Gy/ 15 fr (2.67 Gy daily)	I: 48 Gy/15 fr (3.2 Gy daily) II: 53 Gy/15 fr (3.53 Gy daily)
IMRT MC-2 [43]	Germany	cosmetic outcome	502	50.4 Gy/28 fr (1.8 Gy daily)	/	64.4 Gy/28 fr (2.3 Gy daily)
UZB trial [44]	Belgium	pulmonary/cardiac function arm mobility and lymphedema	123	42 Gy/15 fr (2.8 Gy daily)	/	51/15 fr (3.4 Gy daily)

fr = Fractions.

trial (primary endpoints: cosmetic outcome at 6 weeks and 2 years, and 2-year and 5-year local control) comparing an experimental arm of conventionally fractionated WBRT up to 50.4 Gy/28 fr (1.8 Gy daily) with an integrated boost of 64.4 Gy/28 fr (2.3 Gy daily) vs. a conventional arm employing WBRT of up to 50.4 Gy/28 fr (1.8 Gy daily) and a sequential boost of 16 Gy/8 fr (up to 66.4 Gy) for a total of 36 fractions [43]. Finally, the UZ in Brussels performed a unicenter, non-blinded, randomized trial comparing conventional WBRT (50 Gy/25 fr) and a sequential boost of 16 Gy/8 fr for a total of 66 Gy over 7 weeks vs. an experimental arm of 42 Gy/15 fr (2.8 Gy daily) for WBRT with a SIB of 0.6 Gy daily (up to 51 Gy/15 fr over 3 weeks). Treatments were delivered with tomotherapy, and nodal areas and post-mastectomy patients (who did not receive a boost dose) were included [44]. The short-term toxicity profile was comparable between treatment arms. All these trial will provide evidence on boost integration during WBRT after BCS for early breast cancer. Table 3 summarizes the main characteristics of the available trials.

Final Remarks

The incorporation of the boost dose within either a conventionally fractionated or hypofractionated whole breast phase is definitely an interesting and promising field for clinical investigation [45]. It allows for treatment acceleration and dose escalation in the area of higher risk of relapse. Precise and reliable treatment techniques are mandatory to provide robust dosimetry, accurate delivery, and consistent clinical results. Patients should preferably be enrolled into clinical trials in order to have prospectively collected outcomes in terms of local control, long-term toxicity profile, cosmetic result, and quality of life [46, 47].

Disclosure Statement

The authors disclose no conflict of interest.

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