Clinical and Translational Radiation Oncology 41 (2023) 100651

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Acute skin toxicity of ultra-hypofractionated whole breast radiotherapy with simultaneous integrated boost for early breast cancer

Angel Montero [a,c,1,*], Raquel Ciérvide [a,1], Carmen Cañadillas [a], Beatriz Álvarez [a], Mariola García-Aranda [a], Rosa Alonso [a], Mercedes López [a], Xin Chen-Zhao [a], Leyre Alonso [b], Jeannete Valero [a], Emilio Sánchez [a], Ovidio Hernando [a], Paz García de Acilu [b], Pedro Fernandez-Letón [b], Carmen Rubio [b]

[a] Department of Radiation Oncology, HM Hospitales, Madrid, Spain
[b] Department of Medical Physics, HM Hospitales, Madrid, Spain
[c] Facultad de Ciencias de la Salud, Universidad Camilo José Cela, Madrid, Spain.

ARTICLE INFO

Keywords:
Ultra-hypofractionated radiation treatment
Simultaneous boost
Early breast cancer

ABSTRACT

Background: Whole-breast irradiation (WBI) after breast conserving surgery (BCS) is indicated to improve loco-regional control and survival. Former studies showed that addition of tumor bed boost in all age groups significantly improved local control although no apparent impact on overall survival but with an increased risk of worse cosmetic outcome. Even though shortened regimens in 3 weeks are considered the standard, recent studies have shown the non-inferiority of a treatment regimen of 5 fractions in one-week in both locoregional control and toxicity profile, although simultaneous integrated boost (SIB) in this setting has been scarcely studied.

Materials and Methods: From March-2020 to March-2022, 383 patients with early breast cancer diagnosis and a median age of 56 years-old (range 30–99)were included in a prospective registry of ultra-hypofractionated WBI up to a total dose of 26 Gy in 5.2 Gy/fraction with a SIB of 29 Gy in 5.8 Gy/fraction in 272 patients (71%), 30–31 Gy in 6–6.2 Gy/fraction in 111 patients (29%) with close/focally affected margins. Radiation treatment was delivered by conformal 3-D technique in 366 patients (95%), VMAT in 16patients (4%) and conformal 3-D with deep inspiration breath hold (DIBH) in 4patients (1%). Ninety-three per cent of patients received endocrine therapy and 43% systemic or targeted chemotherapy. Development of acute skin complications was retrospectively reviewed.

Results: With a median follow-up of 18 months (range 7–31), all patients are alive without evidence of local, regional or distant relapse. Acute tolerance was acceptable, with null o mild toxicity: 182 (48%) and 15 (4%) patients developed skin toxicity grade 1 and 2 respectively; 9 (2%) and 2 (0.5%) patients breast edema grade 1and 2 respectively. No other acute toxicities were observed. We also evaluated development of early delayed complications and observed grade 1 breast edema in 6 patients (2%); grade 1 hyperpigmentation in 20 patients (5%); and grade 1 and 2 breast induration underneath boost region in 10(3%) and 2 patients (0.5%) respectively. We found a statistically significant correlation between the median PTV_{WBI} and presence of skin toxicity ($p = 0.028$) as well as a significant correlation between late hyperpigmentation with the median PTV_{BOOST} ($p = 0.007$) and the ratio PTV_{BOOST}/PTV_{WBI} ($p = 0.042$).

Conclusion: Ultra-hypofractionated WBI + SIB in 5 fractions over one-week is feasible and well tolerated, although longer follow-up is necessary to confirm these results.

Abbreviations: BCS, breast conserving surgery; BED, biological effective dose; DIBH, deep inspiration breath hold; IGRT, image-guided radiation treatment; RT, radiation therapy; SIB, simultaneous integrated boost; SLNB, sentinel lymph node biopsy; PTV, planning target volume; VMAT, volumetric modulated arc therapy; WBI, whole breast irradiation.

* Corresponding author at: Department of Radiation Oncology, HM Hospitales, c/Oña 10, 28050 Madrid, Spain.
E-mail address: amontero@hmhospitales.com (A. Montero).

[1] These 2 authors contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.ctro.2023.100651
Received 13 January 2023; Received in revised form 18 May 2023; Accepted 4 June 2023
Available online 15 June 2023

Introduction

Locoregional breast cancer treatment has evolved dramatically in recent decades and ensuring local control is a cornerstone of successful results [1]. Most local relapses after breast conserving surgery and radiation therapy (BCS + RT) develop in the tumor bed or its immediate surrounding area [2–4] and have been associated with an increased risk of distant metastases and reduced breast cancer survival [5], suggesting the benefit of increasing the radiotherapy total dose in these areas through an additional boost to eliminate any remaining subclinical tumor tissue. The randomized trial'boost vs. no boost' of the European Organization for Research and Treatment for Cancer (EORTC 22881–10882) showed significantly improved local control with the addition of tumor bed boost irradiation for invasive breast cancer in all age groups, with a greater absolute reduction of local recurrences in the younger cohort of patients, although this boost was associated with worse long-term cosmetic results [6]. Furthermore, a systematic review including 5 randomized studies and 8,315 patients confirmed the benefit of a boost in the tumor bed on improving local control after BCS for invasive carcinoma, regardless of the age of the patients at diagnosis [7]. In addition, a multicenter study in 10 institutions in the USA, Canada, and France including more than 4,000 women with intraductal breast carcinoma showed a significant benefit in ipsilateral breast tumor relapse survival in all patients irrespective of age or tamoxifen use [8]. The most widespread clinical practice is to administer the boost immediately after the completion of whole breast irradiation (WBI), which is responsible for lengthening the treatment period. However, an approach that is being increasingly implemented is the simultaneous integrated boost (SIB), where the planning target volume (PTV) receives a dose from beams that differ in the total dose and fraction size. It is delivered during WBI and allows for shortening of the overall treatment time.

Moderately hypofractionated WBI with doses of 40–42.5 Gy in 15–16 fractions and a tumor bed boost when indicated should be offered nowadays to any patient for whole breast/chest wall or lymph node irradiation [9,10]. Nevertheless, shortened ultra-hypofractionated radiotherapy schedules using 5 fractions with weekly periodicity (UK Fast trial), every other day (HAI trial), or daily administration (UK Fast-Forward trial) have also proved their feasibility and good tolerance and are gaining interest [11–13].

In this paper, we present our institutional experience of using an ultra-hypofractionated WBI schedule of 5 daily fractions with an SIB on the tumor bed for the treatment of early breast cancer after breast conserving surgery.

Material and methods

Patients

After the publication of the results of the Fast-Forward study and coinciding with the COVID-19 pandemic, we offered all adult patients with early breast cancer the opportunity to enroll in this prospective, observational registry following conserving surgery. The local Ethics and Clinical Research Committee approved this study, and all the patients signed an informed consent document before their inclusion. The primary objective is to analyze the feasibility and tolerance of an ultra-hypofractionated WBI and SIB protocol. Secondary endpoints included ipsilateral breast recurrence and the appearance of late effects. The use and analysis of patients' data are endorsed by the authorization of the Local Ethics and Clinical Research Committee (Ref.: 21.09.1880-GHM). In this analysis, we present the acute complications observed on implementing our treatment scheme of WBI in 5 daily fractions with an SIB.

Radiation treatment

All the patients included underwent WBIup to a total dose of 26 Gy in 5 fractions of 5.2 Gy/day on consecutive days with a simultaneous integrated boost (SIB) up to a total dose of 29 Gy in 5 fractions of 5.8 Gy/day or 30–31 Gy in 5 fractions of 6–6.2 Gy/day where surgical margins are close or focally positive. This schedule was selected in accordance with linear-quadratic (L-Q) formalism: BED = $n \times d \times [1 + d\ (\alpha/\beta] - K \times (T - Tprolong)$, where n = number of fractions; d = dose per fraction (Gy); α/β = a measure of tissue-specific radiosensitivity; and $K \times (T - Tprolong)$ = impact of the tumor repopulation factor calculated according to the product of the biological dose per day that compensates potential cancer tumor cell repopulation (K, expressed in Gy per day and specific for each tissue) by the difference between the total duration of both treatments (T-Tprolong). This schedule was considered to be equivalent to our previous standard fractionation for an SIB of 15 times 3.2–3.4 Gy for anα/β value and a K value of 3.7 Gy and 0.6 Gy/day, respectively [13–15].

Patients were immobilized in the supine position using a breast wing or T-board with the ipsilateral arm raised above the head. Axial images with a thickness of 3 mm were obtained from the level of the mandible and extended below the inframammary fold. CT simulation images were acquired in free breathing in all cases except 4 (1%) in whom deep inspiration breath hold (DIBH) with the Catalyst™ system (C-RAD AB, Uppsala, Sweden) was used, because of anatomical characteristics, to reduce the dose to the heart and lung.

Volumes of interest were defined by using the RayStation® planning system (RaySearch Laboratories, Stockholm, Sweden) and in accordance with ESTRO consensus guidelines [16]. The whole breast was identified on simulation CT from the skin edge and up to the ventral side of the pectoralis major muscle. The whole breast was then cropped 5 mm inside the skin and the lung surface to create the PTV_{WBI}. The surgical bed was identified coinciding with the presence of surgical clips, the area of architectural distortion in the breast tissue and the postoperative surgical seroma to define the PTV_{BOOST} that was limited anteriorly and posteriorly by the PTV_{WBI}. The ipsilateral and contralateral lungs, heart, and contralateral breast were outlined as organs at risk.

Follow-up and evaluation

Acute toxicity was defined as the occurrence of complications during treatment or up to 90 days after completion of treatment. Although late complications can appear after a prolonged latency period of months or years, we established a minimum follow-up of 6 months in the entire series to evaluate the appearance of early delayed side effects. Radiotherapy toxicities were assessed on the last day of treatment, one week after, and one month after radiation treatment compliance and every 3 months thereafter. Toxicities were graded according to the RTOG/EORTC toxicity scale [17] and were reported by physicians (almost fully dedicated to breast cancer) and nurse practitioners.

Pearson's chi-square test for categorical variables was used to compare characteristics among different subgroups regarding toxicity development and statistical significance was considered when $p < 0.05$. Possible associations between toxicity and age, breast volume, boost volume, total dose, radiation modality and the use of chemotherapy or hormonotherapy have been analyzed. SPSS (IBM SPPS Statistics for Windows, Version 19.0 (Armonk, NY; IBM Corp) software was used for calculations.

Results

A total of 383 women with a median age of 56 years old (range 30–99) were treated at our institution between March 2020 and March 2022. All patients underwent a BCS procedure with negative margins in 80% and close (<1 mm for infiltrating carcinoma or < 2 mm for intraductal carcinoma) or focally positive margins in the remaining 20% of the patients. All cases had a pathologically confirmed negative lymph node study by SLNB (pN0(sn)). The patients' complete characteristics are detailed in Table 1.

Table 1
Patients' characteristics.

	N (%)
Median age (range)	56 (66; 30–92)
Median tumor size (range)	12 (54.5; 0.5–55)
pT	
pTis	78 (20.4%)
pT1a	26 (6.8%)
pT1b	87 (22.7%)
pT1c	163 (4,5%)
pT2	29 (7.6%)
SLNB (sentinel lymph node biopsy)	383 (100%)
Breast side	
Left	201 (52.5%)
Right	182 (4.,5%)
Immuno-histochemical molecular subtype	
DCIS	81 (21.1%)
Luminal A	193 (50.4%)
Luminal B HER2-	87 (22.7%)
Luminal B HER2+	16 (4.2%)
HER2-enriched	0 (0%)
Triple negative	6 (1.6%)
Surgical margins	
Negative	310 (81%)
Close/focally positive	73 (19%)
Postoperative seroma	
Yes	46 (12%)
No	337 (88%)
Boost location	
Upper-outer	222 (58%)
Upper-inner	52 (13.6%)
Lower-outer	54 (14%)
Lower-inner	32 (8.4%)
Central	23 (6%)
Chemotherapy/Targeted therapies	
Yes	45 (11.7%)
No	338 (88.3%)
Endocrine therapy	
Yes	357 (93.2%)
No	26(.,8%)

The prescription dose to the whole breast was 26 Gy in 5.2 Gy/fraction on 5 consecutive days. An SIB was administered to all patients up to a total dose of 29 Gy in 5.8 Gy/fraction in 272 patients (71%) and 30–31 Gy in 6–6.2 Gy/fraction in 111 patients (29%) with close/focally positive margins. Radiation treatment was delivered using the conformal 3-D technique with multisegmented tangential fields in 366 patients (96%) and VMAT in 16 patients (4%). In 4 patients, a 3D technique with deep inspiration breath hold (DIBH) was used. The treatment beam arrangement for the SIB comprised 2 coplanar beams in 2 cases (0.6%), 3 beams in 142 cases (37%), 4 beams in 194 cases (51%), 5 beams in 25 cases (7%), 9 beams in 1 case (0.3%) and 2 VMAT-arcs in 16 cases (4%). Assessment and approval of the treatment planning were accomplished based on the target and organs at risk constraints from the Fast Forward protocol. Dose constraints are detailed in Table 2. Patients were treated 5 days per week with daily IGRT (image-guided radiation therapy) verification using LINAC-kV-cone-beam CT and SGRT (surface-guided radiation therapy) based on the Catalyst™ and ExacTrac Dynamic® (Brainlab AG, Munich, Germany) were also used to guide the patient́s set up and assess intrafraction surface movement.

Table 2
Dose constraintsfor organs at risk.

OAR	
Ipsilateral lung	V12 < 20%
Contralateral lung	Dmean < 5.6 Gy
	V3.6 < 10%
Heart	V12 < 5%
	V7 < 5%
	V1.5 < 30%
Contralateral breast	V3.6 < 30 %
Spinal canal	Dmax < 27 Gy
	D0.01 cc < 22.5 Gy

OAR: organs at risk; Dmean: mean dose; Dmax: maximal dose.

Adjuvant chemotherapy and targeted therapies were administered to 43 patients (11%). Chemotherapy schedules were paclitaxel and trastuzumab in 17 patients (4%), doxorubicin and cyclophosphamide followed by paclitaxel in 17 patients (4%), and docetaxel and cyclophosphamide in 9 patients (2%). Ninety-three percent of patients received endocrine therapy, either tamoxifen (41%) or aromatase inhibitors (52%).

All patients completed the planned treatment. The results were analyzed retrospectively according to data extracted from patient́s records. Acute tolerance was acceptable with null or mild toxicity. The development of acute radiation dermatitis (erythema and desquamation) was the most prevalent acute complication: 182 patients (48%) developed grade 1 and 15 patients (4%) had grade 2 toxicity. The acute breast edema was grade 1 in 9 patients (2%) and grade 2 in 2 patients (0.5%). No other acute toxicities were observed. The long-term outcomes observed were acceptable with few patients experiencing early chronic complications and which were mild in most cases: grade 1 breast edema in 6 patients (2%); grade 1 breast hyperpigmentation on the boost area in 20 patients (5%) and grade 1 or 2 early delayed indurations underneath the boost area in 10 patients (3%) and 2 patients (0.5%) respectively. With a median follow-up of 18 months (range 7–31), all patients are alive with no evidence of local or distant relapse.

A comparative chi-square test of the factors related to toxicity developmentwas performed (Table 3). For analytical purposes, we also calculated median volumes of PTV_{WBI}(mPTV_{WBI}, 725 cm3 (range 114–2409 cm3)) and PTV_{BOOST}(mPTV_{BOOST}, 28 cm3 (range 4.6–198 cm3)).We found a statistically significant correlation between the mPTV_{WBI} and the presence of acute erythema or desquamation ($p = 0.028$) as well as a significant correlation between late hyperpigmentation with the mPTV_{BOOST} ($p = 0.007$) and the ratio PTV_{BOOST}/PTV_{WBI}($p = 0.042$).

Discussion

In recent years, results from several large population-based studies have suggested that WBI after BCS could offer survival advantages over mastectomy, and a recent *meta*-analysis including 1,311,600 patients from 25 studies indicates that BCS + RT is associated with higher survival rates compared to mastectomy and should be the choice for early breast cancer (T1-2 N0-1), whenever possible [18–22].

The use of an SIB as part of WBI, although it increases the complexity of radiotherapy plans, might offer some advantages including radiobiological benefits, by reducing the risk of treatment failure [15]; dosimetric advantages, by improving dose homogeneity in the boost PTV and facilitating dose escalation in the tumor bed and logistic benefits on improving quality of life by reducing the overall treatment time and favoring patients' compliance. Table 4 summarizes different studies that focus on the safety and feasibility of WBI with an SIB using moderate hypofractionation [23–37].

Although several studies support the routine use of a SIB, there are still few randomized studies, and some have only been reported as conference abstracts. Van Parijs et al. reported no differences in acute skin tolerance in a randomized trial using a normofractionated regimen with a sequential boost or with moderate hypofractionation and a simultaneous boost [27]. The Paelinck et al. group observed a significantly higher incidence of acute grade 2/3 skin toxicity with a sequential boost as compared to SIB [30]. The results of the randomized IMRT-MC2 trial that compared an intensity-modulated radiotherapy scheme with SIB versus the same scheme with 3D conformal radiotherapy and a sequential boost concluded that there were no differences concerning late cosmesis appearance (2-year follow-up) although IMRT-SIB was slightly superior to 3D-CRT with a sequential boost in quality of life by shortening overall treatment time [38,39]. Results from the IMPORT-High trial suggested that a SIB is a safe approach that allows a

Table 3
Results of Pearson'schi-square comparative analysis for acute and late toxicity.

	ACUTE		EARLY DELAYED		
	Breast dermatitis	Breast edema	Breast edema	Boost hyperpigmentation	Boost induration
	p	p	p	p	p
Age: <56 vs > 56 yo	0.337	0.081	0.082	0.226	0.340
$mPTV_{WBI}$:<725 cm vs. > 725 cm	0.028	0.301	0.80	0.846	0.989
$mPTV_{BOOST}$: <28 cm vs. < 28 cm	0.439	0.623	0.105	0.007	0.168
Ratio PTV_{BOOST}/PTV_{WBI}: <0.4 vs. > 0.4	0.495	0.869	0.496	0.042	0.220
Chemotherapy: yes vs. no	0.688	0.484	0.378	0.101	0.871
Endocrine therapy: yes vs. no	0.891	0.934	0.792	0.826	0.987
Radiation technique: 3D vs. VMAT	0.794	0.990	0.565	0.984	0.996
Postoperative breast seroma: yes vs. no	0.933	0.943	0.390	0.885	0.998

reduced number of hospital visits [40]. Finally, the recently reported results of the RTOG 1005 trial showed that the use of a scheme with moderate hypofractionation and SIB is not inferior in terms of the local recurrence rate compared to an irradiation scheme with conventional fractionation and a sequential boost and that there is no difference in toxicity or cosmetic outcome [41].

However, unlike what happens with moderate hypofractionation, few ultra-hypofractionated regimens deliver a SIB. In the FAST-Forward trial, the tumor bed boost was delivered sequentially, administering 10–16 Gy in 5 additional fractions in as much as 25% of the patients [12]. Recently, the Machiels et al. group published the results observed in 102 patients using a radiotherapy schedule identical to FAST-Forward but with a single fraction sequential boost of 6 Gy in those patients who needed it. The incidence of grade 1 and 2 acute skin toxicity was 74% and 2.7%, respectively [42]. In contrast, the HAI5 trial analyzed acute tolerance of a 5-fraction schedule on every other day for 12 days in 95 breast cancer patients who received 28.5 Gy/5.7 Gy on the breast/chest wall and 27 Gy/5.4 Gy on the lymph node areas when indicated with an SIB in 66% of patients of 32.5 Gy/6.5 Gy or 34.5 Gy/6.9 Gy depending on the surgical margins. With a median follow-up of 5.6 months, the authors reported an incidence of grade 2–3 acute skin toxicity of 17.6% in the SIB arm versus 0% when a SIB was not administered [11]. From the same group, the YO-HAI5 (Young-Old Highly Accelerated Irradiation in 5 fractions) trial randomized breast cancer patients after a lumpectomy to WBI in 5 fractions of 5.7 Gy and a SIB of 6.2 Gy in 12 days or WBI in 15 fractions of 2.67 Gy with a simultaneous boost of 3.12 Gy/day. The authors observed a significantly higher incidence of acute breast edema, breast pain, asthenia, and skin toxicity in those patients treated with moderate hypofractionation as compared to ultra-hypofractionation [31].

Our treatment protocol includes the use of a 5-day ultra-hypofractionated scheme of WBI + SIB after a breast lumpectomy. Our results coincide with the good acute tolerance of a SIB, even when an ultra-hypofractionated scheme is used. However, due to the small number of patients and the few events observed, we have been unable to demonstrate any significant association between the incidence of acute skin toxicity with different factors related to the characteristics of the patients or the treatment. A plausible explanation for the good tolerance observed would be the use of the tangential field technique with multisegmented conformal WBI, the so-called 'forward-planned IMRT', and the beam arrangement used for anSIB employing 3 or 4 beams in 88% of patients. This complexity in planning might justify a benefit in dose homogeneity and good acute tolerance. Due to the short follow-up of our series, we have been unable to assess late changes in the breast and their possible influence on the cosmetic results, beyond the evaluation of early delayed complications regarding breast edema, changes in pigmentation, and induration of the boost area. To date, some studies using ultra-hypofractionated regimens have reported long-term complication results. Thus, in the FAST-Forward study, no significant differences were observed in the physician's assessment of late effects between schemes of 40 Gy in 15 fractions versus 26 Gy in 5 fractions ($p = 0.17$) [12]. Van Heulle et al. analyzed the 2-year toxicity results of the HAI5 study and compared them utilizing a matched-case analysis with the results from a similar group of patients treated with a moderate hypofractionated regimen in 15 fractions. Researchers reported a significantly lower incidence of retraction and telangiectasias in the breast with ultra-hypofractionation although a higher incidence of fibrosis outside the tumor bed [43]. The same group compared the health-related quality of life of the patients treated in different studies evaluating irradiation schemes of 5 or 15 fractions. The authors reported that patients treated with 5-fraction schemes had a significantly lower deterioration in health-related quality of life after 1 year ($p = 0.006$) as well as a significant reduction in late complications in the arm and breast ($p < 0.0001$) [44]. Finally, Sigaudi et al. reported a good/excellent cosmetic outcome 6 months after radiotherapy in 45 patients with low-risk breast cancer following conservative surgery treated with a schedule of 26 Gy in 5 fractions over 1 week, although no patients received a boost [45].

We are aware of the weaknesses and controversial aspects of our work. The retrospective nature of this analysis and the absence of randomization and a control arm may affect the interpretation of the data, although comparison with historical series does not suggest worse tolerance with ultrahypofractionated WIB + SIB. Besides, the per-protocol decision to administer a boost to all patients might be debatable, and although evidence supports its benefit in reducing local failure for all treated patients, the improvements in local control achieved in recent decades as well as the negative impact that a boost can have on the cosmetic outcome reinforce the tendency to deliver it only to patients at high risk of local recurrence. Furthermore, the low number of patients and short follow-up could mask some results and make it impossible to establish long-term tolerance with certainty. In addition, the assessment of the toxicity and cosmesis of our series was registered only by physicians and nurse practitioners. It would have been highly valuable to know the patient-reported clinical outcomes (PRCO) and their degree of satisfaction with their results. Although overall feedback is good, it is not adequately reported by personalized PRCO and results cannot be generalized. Finally, it could be argued that most of the patients included are low or very low risk, and they would have been suitable for treatment with partial breast irradiation, something on which we fully agree. However, many PBI regimens lengthen the duration of treatment up to 2 weeks, so a well-tolerated WBI regimen in a single week could be of interest to these patients.

Conclusion

In recent years, the idea of "less is more" has been positioned as a cornerstone in the treatment of breast cancer. Reducing the length and intensity of current treatments without decreasing their effectiveness is a goal for therapeutic advances. With moderate hypofractionation already assumed as a standard, ultra-hypofractionated radiotherapy regimens that allow the total duration of treatment to be shortened even more are emerging as an attractive option. Despite the intrinsic limitations of the study, our experience with the 5-day ultra-hypofractionated scheme of WBI + SIB in patients with early breast cancer after breast

Table 4
Acute and late skin and subcutaneous tissue toxicities reported with hypofractionated WBI + SIB.

Author/year	Type of study	n	MFU (months)	RT schedule	ChT	ET	Acute skin toxicity	Late skin and subcutaneous tissue toxicity
Formenti 2007 [23]	Prospective	91	12	WBI: 40.5 Gy@2.7 Gy SIB: 48 Gy@3.2 Gy	33.30%	80%	G0-1: 58.55% G2: 8.1% G3: 0.9%	G3-4: 0
Freedman 2007 [24]	Prospective	75	69	WBI: 45 Gy@2.25 Gy SIB: 56 Gy@2.8 Gy	44%	69%	G0-1: 77% G2: 23%	NR
Morganti 2009 [25]	Retrospective	332	31	A: WBI: 50.4 Gy@1.8 Gy SeqB: 10 Gy@2Gy B: WBI: 40 Gy@2.5 Gy SIB: 44 Gy@2.75 Gy C: WBI: 50 Gy@2Gy SIB: 60 Gy@2.4 Gy	A: 64.9% B: 38.4% C: 76.5%	A: 63.4% B: 77.8% C: 69.6%	A: G2: 33.6% G3: 3.1% B: G2: 13.1% G3: 1% C: G2: 45.1% G3: 2%	NR
Cante 2011 [26]	Prospective	463	60	WBI: 45 Gy@2.25 Gy SIB: 50 Gy@2.5 Gy	27%	90%	G0-1: 68% G2: 30% G3: 2%	G1: 18% G2: 2%
Van Parijs 2012 [27]	Randomized	69	28	A: WBI: 50 Gy@2Gy SeqB: 66 Gy@2Gy B: WBI: 42 Gy@2.8 Gy SIB: 51 Gy@3.4 Gy	53%	80%	A: G0-1: 71.85% G2: 21.9% G3: 6.25% B: G0-1: 64.9% G2: 27% G3: 8.1% p = 0.94	G ≥ 1: 60% (A) vs. 30% (B), p = 0.056
Franco 2014 [28]	Prospective	82	12	WBI: 45 Gy@2.25 Gy SIB: 50 Gy@2.5 Gy	25%	79%	G0 41 %; G1 53 %; G2 6 %; G3 < 1 %	G2 fibrosis 2 % G2 hyperpigmentation 2 %
De Rose 2016 [29]	Prospective	144	24	WBI: 40.5 Gy@2.7 Gy SIB: 48 Gy@3.2 Gy	15%	83%	G2: 8%	G1: 14%
Paelinck 2017 [30]	Randomized	167	NR	A: WBI: 40,05 Gy@2.678 Gy SIB: 46.8–49.95 Gy@3.12–3.33 Gy B: WBI: 40.05 Gy@2.678 Gy SeqB: 10–14.88 Gy@2.5–2.48 Gy	51.50%	85%	A: G2-3: 29% B: G2-3: 46% p = 0.037	(n = 150) G3-4: 0
Van Hulle 2021 [31]								
Bautista 2018 [32]	Retrospective	34	48	WBI: 45 Gy@2.25 Gy SIB: 56 Gy@2.8 Gy	53%	77%	G0: 53% G1: 47%	G1: 6%
Fiorentino 2019 [33]	Retrospective	80	45	A: WBI: 50 Gy@2Gy SIB: 60 Gy@2.4 Gy B: WBI: 40.5 Gy@2.7 Gy SIB: 48 Gy@3.2 Gy	8.75%	91.25%	A: G1: 62.5% G2: 25% B: G1: 52.5% G2: 2.5%	G1: 19%
Lertbutsayanukul 2020[34]	Retrospective	114	86	A: WBI: 50 Gy@2Gy SIB: 65 Gy@2.6 Gy B: WBI: 43.2 Gy@2.7 Gy SIB: 52.8 Gy@3.3 Gy	53.50%	83%	A: G1-2: 91.3% B: G1-2: 73.7% p = 0.048	G1-2: 100%
Krug 2020 [35]	Randomized	446	NR	A: IMRT WBI: 50.4 Gy@1.8 Gy SIB: 64.4 Gy@2.3 Gy B: 3DCRT WBI: 50.4 Gy@1.8 Gy SeqB: 16 Gy@2Gy	43.50%	NR	A: G2: 29.1% G3: 3.5% B: G2: 20.1% G3: 2.3% p = 0.02	NR
Dong 2021 [36]	Retrospective	185	26	A: WBI: 42.56 Gy@2.66 Gy SIB: 48 Gy@3Gy B: WBI: 50 Gy@2Gy SeqB: 10 Gy@2Gy	70%	76%	A: G0-1: 82% G2-4: 18% B: G0-1: 70% G2-4: 30%	A: G0-1: 94% G2-4: 6% B: G0-1: 96% G2-4: 4%
Pfaffendorf 2022 [37]	Prospective	274	60	WBI: 40 Gy@2.5 Gy SIB: 48 Gy@3Gy	37%	87%	NR	G1: 28% G2: 7.3% G3: 0.7%

MFU: median follow-up; RT: radiation therapy; ChT/TT: chemotherapy/targeted therapy; ET: endocrine therapy; WBI: whole breast irradiation; SIB: simultaneous boost; SeqB: sequential boost; NR: not reported.

conserving surgery makes us consider this approach feasible and well tolerated with acceptable acute skin tolerance and good treatment compliance. However, further well-designed studies with longer follow-up are needed to confirm these outcomes.

Funding

This research received no external funding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

To Alyson Kim Turner, for reviewing, revising and editing this manuscript for English Language grammar and syntax.

References

[1] Recht A, Solin LJ. Breast-conserving surgery and radiotherapy in early-stage breast cancer: the importance of local control. SeminRadiatOncol 2011;21(1):3–9. https://doi.org/10.1016/j.semradonc.2010.08.001.
[2] Fisher B, Wickerham DL, Deutsch M, Anderson S, Redmond C, Fisher ER. Breast tumor recurrence following lumpectomy with and without breast irradiation: an overview of recent NSABP findings. SeminSurgOncol 1992;8(3):153–60.
[3] Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. Ann Oncol 2001 Jul;12(7):997–1003. https://doi.org/10.1023/a:1011136326943.
[4] Botteri E, Bagnardi V, Rotmensz N, Gentilini O, Disalvatore D, Bazolli B, et al. Analysis of local and regional recurrences in breast cancer after conservative surgery. Ann Oncol 2010 Apr;21(4):723–8. https://doi.org/10.1093/annonc/mdp386.
[5] Veronesi U, Marubini E, Vecchio MD, Manzari A, Andreola S, Greco M, et al. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. J Natl Cancer Inst 1995;87(1):19–27.
[6] Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. European organisation for research and treatment of cancer radiation oncology and breast cancer groups. whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. LancetOncol 2015;16(1):47–56. https://doi.org/10.1016/S1470-2045(14)71156-8.
[7] Kindts I, Laenen A, Depuydt T, Weltens C. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane DatabaseSyst Rev 2017;11(11):CD011987.
[8] Moran MS, Zhao Y, Ma S, Kirova Y, Fourquet A, Chen P, et al. Association of radiotherapy boost for ductal carcinoma in situ with local control after whole-breast radiotherapy. JAMA Oncol 2017;3(8):1060–8. https://doi.org/10.1001/jamaoncol.2016.6948.
[9] Meattini I, Becherini C, Boersma L, Kaidar-Person O, Marta GN, Montero A, 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(1):e21–31. https://doi.org/10.1016/S1470-2045(21)00539-8.
[10] Shah C, Al-Hilli Z, Vicini F. Advances in breast cancer radiotherapy: implications for current and future practice. JCO OncolPract 2021;17(12):697–706. https://doi.org/10.1200/OP.21.00635.
[11] Agrawal RK, Alhasso A, et al. First results from the UK randomized FAST trial of hypofractionation with radiotherapy for the treatment of early breast cancer (CRUKE/04/015). RadiotherOncol 2011;100:93–100. FAST Trialists Group.
[12] Monte C, Lievens Y, Olteanu LAM, Paelinck L, Speleers B, Deseyne P, et al. Highly accelerated irradiation in 5 fractions (HAI-5): Viability in older women with early or locally advanced breast cancer. Int J RadiatOncolBiol Phys 2017;98(4):922–30. https://doi.org/10.1016/j.ijrobp.2017.01.229.
[13] Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. FAST-forward Trial management group. hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395(10237):1613–26.
[14] Azria D, Hennequin C, Giraud P. Compensation de la dosetotale en cas d'interruptiontemporaire de radiothérapie externe dans le contexte de la pandémie de COVID-19. mise aupointpratiqueCancerRadiother 2020;24(3):182–7. https://doi.org/10.1016/j.canrad.2020.04.001.
[15] Haviland JS, Bentzen SM, Bliss JM, Yarnold JR. Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: An analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation. RadiotherOncol 2016;121(3):420–3.
[16] Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. RadiotherOncol 2015;114(1):3–10. https://doi.org/10.1016/j.radonc.2014.11.030.
[17] Cox JD, Stetz JoAnn, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the european organization for research and treatment of cancer (EORTC). Int J RadiatOncolBiolPhys 1995;31(5):1341–6.
[18] Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg 2014;149(3):267–74. https://doi.org/10.1001/jamasurg.2013.3049.
[19] vanMaaren MC, de Munck L, de Bock GH, Jobsen JJ, van Dalen T, Linn SC, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. Lancet Oncol 2016;17(8):1158–70. https://doi.org/10.1016/S1470-2045(16)30067-5.
[20] Christiansen P, Carstensen SL, Ejlertsen B, Kroman N, Offersen B, Bodilsen A, et al. Breast conserving surgery versus mastectomy: overall and relative survival-a population based study by the danish breast cancer cooperative group (DBCG). Acta Oncol 2018;57(1):19–25. https://doi.org/10.1080/0284186X.2017.1403042.
[21] de Boniface J, Szulkin R, Johansson ALV. Survival after breast conservation vs mastectomy adjusted for comorbidity and socioeconomic status: a swedish national 6-year follow-up of 48 986 women. JAMA Surg 2021;156(7):628–37. https://doi.org/10.1001/jamasurg.2021.1438.
[22] Christiansen P, Mele M, Bodilsen A, Rocco N, Zachariae R. Breast-conserving surgery or mastectomy?: impact on survival. Ann Surg Open 2022;3(4):e205.
[23] Formenti SC, Gidea-Addeo D, Goldberg JD, Roses DF, Guth A, Rosenstein BS, et al. Phase I-II trial of prone accelerated intensity modulated radiation therapy to the breast to optimally spare normal tissue. J ClinOncol 2007;25(16):2236–42. https://doi.org/10.1200/JCO.2006.09.1041.
[24] Freedman GM, Anderson PR, Goldstein LJ, Ma CM, Li J, Swaby RF, et al. Four-week course of radiation for breast cancer using hypofractionated intensity modulated radiation therapy with an incorporated boost. Int J RadiatOncolBiol Phys 2007;68(2):347–53. https://doi.org/10.1016/j.ijrobp.2006.12.035.
[25] Morganti AG, Cilla S, Valentini V, Digesu' C, Macchia G, Deodato F, et al. Phase I-II studies on accelerated IMRT in breast carcinoma: technical comparison and acute toxicity in 332 patients. RadiotherOncol 2009;90(1):86–92. https://doi.org/10.1016/j.radonc.2008.10.017.
[26] Cante D, Rosa La Porta M, Casanova-Borca V, Sciacero P, Girelli G, Pasquino M, et al. Accelerated hypofractionated adjuvant whole breast radiotherapy with concomitant photon boost after conserving surgery for early stage breast cancer: a prospective evaluation on 463 patients. Breast J 2011;17(6):586–93.
[27] Van Parijs H, Miedema G, Vinh-Hung V, Verbanck S, Adriaenssens N, Kerkhove D, et al. Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial. RadiatOncol 2012;1(7):80. https://doi.org/10.1186/1748-717X-7-80.
[28] Franco P, Cante D, Sciacero P, Girelli G, La Porta MR, Ricardi U. Tumor bed boost integration during whole breast radiotherapy: a review of the current evidence. Breast Care (Basel) 2015;10(1):44–9. https://doi.org/10.1159/000369845.
[29] De Rose F, Fogliata A, Franceschini D, Navarria P, Villa E, Iftode C, et al. Phase II trial of hypofractionated VMAT-based treatment for early stage breast cancer: 2-year toxicity and clinical results. RadiatOncol 2016;11(1):120. https://doi.org/10.1186/s13014-016-0701-z.
[30] Paelinck L, Gulyban A, Lakosi F, Vercauteren T, De Gersem W, Speleers B, et al. Does an integrated boost increase acute toxicity in prone hypofractionated breast irradiation?. A randomized controlled trial. RadiotherOncol 2017;122(1):30–6. https://doi.org/10.1016/j.radonc.2016.12.023.
[31] Van Hulle H, Vakaet V, Monten C, Deseyne P, Schoepen M, Colman C, et al. Acute toxicity and health-related quality of life after accelerated whole breast irradiation in 5 fractions with simultaneous integrated boost. Breast 2021;55:105–11.
[32] Bautista Hernandez MY, Lujan Castilla PJ, Quézada Bautista AA. Hypofractionation with concomitant boost using intensity-modulated radiation therapy in early-stage breast cancer in Mexico. Rep PractOncolRadiother 2018;23(4):276–83.
[33] Fiorentino A, Gregucci F, Mazzola R, Figlia V, Ricchetti F, Sicignano G, et al. Intensity-modulated radiotherapy and hypofractionated volumetric modulated arc therapy for elderly patients with breast cancer: comparison of acute and late toxicities. RadiolMed 2019;124(4):309–14. https://doi.org/10.1007/s11547-018-0976-2.
[34] Lertbutsayanukul C, Pitak M, Ajchariyasongkram N, Rakkiet N, Seuree F, Prayongrat A. Long-term patient-rated cosmetic and satisfactory outcomes of early breast cancer treated with conventional versus hypofractionated breast irradiation with simultaneous integrated boost technique. Breast J 2020;26(10):1946–52. https://doi.org/10.1111/tbj.13960.
[35] Krug D, Baumann R, Krockenberger K, et al. Adjuvant hypofractionated radiotherapy with simultaneous integrated boost after breast-conserving surgery: results of a prospective trial. StrahlentherOnkol 2021;197:48–55. https://doi.org/10.1007/s00066-020-01689-.
[36] Dong J, Yang Y, Han D, Zhao Q, Liu C, Sun H, et al. Hypofractionated simultaneous integrated boost radiotherapy versus conventional fractionation radiotherapy of early breast cancer after breast-conserving surgery: clinical observation and analysis. Technol Cancer Res Treat 2021. https://doi.org/10.1177/15330338211064719.
[37] Pfaffendorf C, Vonthein R, Krockenberger-Ziegler K, Dellas K, Schreiber A, Uhlemann D, et al. Hypofractionation with simultaneous integrated boost after breast-conserving surgery: Long term results of two phase-II trials. Breast 2022;64:136–42. https://doi.org/10.1016/j.breast.2022.05.008.
[38] Hörner-Rieber J, Forster T, Hommertgen A, Haefner MF, Arians N, König L, et al. Intensity modulated radiation therapy (IMRT) with simultaneously integrated boost shortens treatment time and is non inferior to conventional radiation therapy followed by sequential boost in adjuvant breast cancer treatment: results of a large randomized phase III trial (IMRT-MC2 trial). Int J RadiatOncolBiol Phys 2021;109(5):1311–24. https://doi.org/10.1016/j.ijrobp.2020.12.005.
[39] Forster T, Hommertgen A, Häfner MF, Arians N, König L, Harrabi SB, et al. Quality of life after simultaneously integrated boost with intensity-modulated versus conventional radiotherapy with sequential boost for adjuvant treatment of breast cancer: 2-year results of the multicenter randomized IMRT-MC2 trial. RadiotherOncol 2021;163:165–76. https://doi.org/10.1016/j.radonc.2021.08.019.
[40] Coles C, Haviland JS, Kirby AM, Bhattacharya I, Brunt AM, Chan C, et al. IMPORT HIGH trial: dose escalated simultaneous integrated boost radiotherapy in early breast cancer. RadiatOncol 2022;161:S197–9. https://doi.org/10.1016/S0167-8140(21)06840-7.
[41] Vicini FA, Winter K, Freedman GM, Arthur DW, Hayman JA, Rosensteinn BS, et al. NRG RTOG 1005: A phase III trial of hypo fractionated whole breast irradiation

with concurrent boost vs. conventional whole breast irradiation plus sequential boost following lumpectomy for high risk early-stage breast cancer. Int J RadiatonOncolBiolPhys 2022;114(3S):S1. https://doi.org/10.1016/j.ijrobp.2022.07.2320.

[42] Machiels M, Weytjens R, Bauwens W, Vingerhoed W, Billiet C, Huget P, et al. Accelerated adaptation of ultrahypofractionated radiation therapy for breast cancer at the time of the COVID-19 pandemic. Clin Oncol 2021;33(3):e166–71.

[43] Van Hulle H, Vakaet V, Deckmyn K, Monten C, Paelinck L, Van Greveling A, et al. Two-year toxicity of hypofractionated breast cancer radiotherapy in five fractions. Acta Oncol 2020 Jul;59(7):872–5. https://doi.org/10.1080/0284186X.2020.1747638.

[44] Van Hulle H, Vakaet V, Bultijnck R, Deseyne P, Schoepen M, Van Greveling A, et al. Health-related quality of life after accelerated breast irradiation in five fractions: a comparison with fifteen fractions. Radiother Oncol 2020;151:47–55.

[45] Sigaudi V, Zannetti M, Ferrara E, Manfredda I, Mones E, Loi G, et al. Ultra-hypofractionation for whole-breast irradiation in early breast cancer: interim analysis of a prospective study. Biomedicines 2022;10(10):2568. https://doi.org/10.3390/biomedicines10102568.