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The role of the radiation therapy breast boost in the 2020s

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ABSTRACT

Given that most local relapses of breast cancer occur proximal to the original location of the primary, the delivery of additional radiation dose to breast tissue that contained the original primary cancer (known as a "boost") has been a standard of care for some decades. In the context of falling relapse rates, however, it is an appropriate time to re-evaluate the role of the boost. This article reviews the evolution of the radiotherapy boost in breast cancer, discussing who to boost and how to boost in the 2020s, and arguing that, in both cases, less is more.

1. Introduction

The concept of a tumour bed boost following wide local excision surgery and whole breast radiotherapy was born in the 1970s, based on the observation in multiple clinical studies that the vast majority of ipsilateral breast tumour recurrences arose in the vicinity of the original index lesion [1,2]. This concept was reinforced by results of detailed histopathological examination of mastectomy specimens by Holland in the 1980s, describing that 60% of patients had cancer cells within 2 cm of the edge of the primary tumor, with only a minority (11%) of patients having cancer cells as far as 4 cm away from the edge of the primary tumor, independent of tumor size [3]. Between 1986 and 1998, five trials randomizing 8325 women to an additional "boost" of radiation to the breast tissue closest to the primary cancer versus no boost were conducted, testing different doses ranging from 45Gy to 50Gy to the whole breast, and an additional boost to the surgical bed ranging from 10 to 25 Gy [4–10]. These trials are discussed in turn below.

In the Lyon trial, which recruited from 1986 to 1992, 1024 women with early breast carcinoma were treated by local excision, axillary dissection, and conventional 50-Gy irradiation given in 25 fractions over 5 weeks and then randomly assigned to receive either no further treatment or a boost of 10 Gy by electrons to the tumor bed. The median follow-up time was 3.3 years. This trial demonstrated that delivery of a boost of 10 Gy in 4 fractions to the tumor bed after 50 Gy in 25 fractions to the whole breast following conservative surgery significantly reduced the risk of early local recurrence albeit the clinical significance of the difference might be considered as minimal (4.5% local recurrence in the no boost arm versus 3.6% in the boost arm). The boost came with a cost of an increased rate of clinician-reported toxicity (12.4% grade 1 and 2 telangiectasia in the boost arm versus 5.9% in the no boost arm) [4]. [see Table 1].

In the Budapest trial, recruiting from 1995 to 1998, 207 women with stage I-II breast cancer who underwent BCS were treated by 50 Gy irradiation to the whole breast and then randomly assigned to receive either a boost to the tumor bed (n = 104) or no further radiotherapy (n = 103). Boost treatments consisted of either 16 Gy electron irradiation (n = 52) or 12–14,25 Gy high dose rate brachytherapy (n = 52). Breast cancer-related events, side effects, and cosmetic results were assessed. At a median follow-up of 5.3 years, the crude rate of local recurrences was 6.7% with and 15.5% without boost. There was no significant difference in local tumor control between patients treated with electron or HDR. The incidence of grade 2–3 side effects was higher in the boost arm (17.3% vs. 7.8%). However, the rate of excellent/good cosmetic results was similar for the two arms (85.6% vs 91.3%) [5].

An Australian study randomised 688 patients from 1996 onwards with histologically proven Tis-2, N0–1, M0 carcinoma to the control arm of 50 Gy in 25 fractions versus the boost arm of 45 Gy in 25 fractions to the whole breast followed by a 16 Gy in 8 fraction electron boost. The total dose to the tumour bed was significantly lower compared to the other trials and in-situ carcinomas were included in the dataset. This trial demonstrated, at a median follow-up of 8.5 years a 2% local recurrence rate in the control arm versus a 4.4% rate in the boost arm, suggesting that the reduced whole breast dose negates the benefit of radiotherapy boost. Five-year cosmetic outcomes were assessed subjectively by a panel in 385 patients and objectively using relative breast retraction assessment. The results showed that the negative cosmetic

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impact of a 16-Gy boost is offset by a lower whole-breast dose of 45 Gy [6,7].

The Nice trial, conducted from 1987 to 1994, randomised 664 patients with invasive breast cancer treated by conservative surgery and axillary dissection and 50Gy in 25 fraction delivered using a telecobalt device to no boost (group A) versus an additional 10 Gy dose to the tumor bed (group B). At a median follow-up of 6 years, there was no significant difference in terms of local recurrence rate between the two groups (6.8% local recurrence rate in group A versus 4.3% in group B) [8].

Around this time, some argued that the radiotherapy boost was not critical to achieve adequate local control as long as tumour resection margins were free of cancer. Against this backdrop was devised the European Organization for Research and Treatment for Cancer (EORTC) randomised trial of boost versus no boost, which recruited from 1989 to 1996 and which demonstrated significantly improved local control with the addition of tumour bed boost irradiation in all age groups with greater absolute reduction of local recurrences in the younger cohort of patients but, again, at the expense of increased toxicity in those treated with a boost [9,10]. At 10 years' median follow-up, the cumulative incidence of local recurrence was 10.2% versus 6.2% for the no boost and the boost group respectively but, again, at the expense of significantly increased severe fibrosis in the boost group (10-year rate of severe fibrosis 4.4% versus 1.6% for boost versus no boost). The absolute local recurrence risk reduction at 10 years was greatest in patients ≤40 years of age: 23.9%–13.5%. No survival benefit from the tumour bed boost was observed. 20-year overall survival was 59.7% (99% CI 56.3–63.0) in the boost group versus 61.1% (57.6–64.3) in the no boost group, hazard ratio (HR) 1.05 (99% CI 0.92–1.19, p = 0.323). This trial has provided a wealth of data as well as a basis for further clinical trials from which to derive recommendations on who should be boosted and how. These aspects are discussed in detail in the next two sections.

2. Who to boost?

2.1. Invasive carcinoma

Since there is no survival benefit and an increased risk of toxicity, it is

Table 1
Technical radiotherapy details of largest (n > 1000) randomised controlled trials of tumour bed boost in patients with invasive or pre-invasive breast carcinoma.

Trial and randomisation	N	Eligibility (years recruiting)	Techniques used	CTV definition for external beam RT	CTV to PTV margin	Whole breast dose	Sequential boost dose	SIB dose (if applicable)	5-year local relapse rate	5-year toxicity rate
Lyon RCT (Boost versus no boost) Romestaing 1997 [4]	1024	Age <70 yrs T ≤ 3 cm, tumour clear of ink (1986–1992)	Electrons	9 or 12 MeV electrons Mean field size 8*8 cm centred on TB	Not specified	50 Gy/25#	10 Gy/4#	NA	*At* 5 yrs, 3.6% (boost) versus 4.5% (no boost)	5-year rate of clinician-reported telangiectasia higher in boost group (12%) than no boost group (6%)
EORTC Boost (Boost versus no Boost) Bartelink 2007 [9], Bartelink 2015 [10]	2657	Any age, T1-2, N0-1 with macroscopically completely excised primary tumour at BCS (1989–1996)	90% electrons or photons 10% IB	"Boost volume" was site of the primary tumour plus 15 mm	NA	50 Gy/25#	16 Gy/8#	NA	*At* 10 yrs, 6.2% (boost) versus 10.2% (no boost)	10-year clinician-reported moderate to severe fibrosis 28.1% (boost) versus 13.2% (no boost)
Young Boost (High dose versus standard dose boost) Brouwers 2018 [11], Bosma 2021 [12]	2421	Age ≤50yrs with pT1-2pN0-2a invasive breast cancer (2004–2011)	95% electrons or photons. 5% IB	15 mm around original tumour defined using pre-op clinical/imaging findings and tumour bed clips	5 mm	50 Gy/25# (for patients treated sequentially)	Standard dose 16 Gy/8# vs high dose 26 Gy/13# (2 Gy per week to boost volume followed by 16 Gy/8# sequentially)	Standard dose 50.68y/28# to WB with 64.4 Gy/28# to boost volume. High dose 51.46 Gy/31# to WB with 73.78 Gy/31# to boost volume	1.1% in both arms	At 4 years, 19% clinician-scored moderate to severe fibrosis in standard dose arm and 39% in high dose arm
IMPORT High (Sequential boost versus SIB) Coles 2021 [13]	2617	T1-3pN0-3a treated with BCS (2009–2015)	Forward or inverse-planned IMRT	Tumour bed clips plus architectural distortion	5 mm	40 Gy/15# (for patients treated sequentially)	16 Gy/8#	36 Gy/15F to WB, 40 Gy to partial breast & 48 Gy or 53 Gy in 15F SIB to TB	1.9% (seq) 2.0% (48 Gy) 3.2% (53 Gy)	11.5% clinician-reported induration (seq), 10.6% (48 Gy), 15.5% (53 Gy)
BIG 3–07/TROG 07.01) DCIS (Boost versus no boost in DCIS) Chua 2022 [14]	1608	Non low-risk DCIS (one or more of age <50yrs, palpable tumour, T ≥ 15 mm, multifocal, IG/HG, comedo/necrosis) (2007–2014)	Electrons or photons	Seroma cavity and/or tumour bed clips plus 10 mm	5–10 mm	50 Gy/25# or 42.5 Gy/16#	16 Gy/8#	NA	7.3% (no boost) and 2.9% (boost)	≥G2 clinician-reported induration 14% (boost) and 6% (no boost)

RT = radiotherapy; BCS = breast conservation surgery; # = fraction; IB = interstitial brachytherapy; IG/HG = intermediate or high grade; TB = tumour bed; WB = whole breast.

important to define which patients will benefit most from a boost. Several studies have identified risk factors for local relapse, including young age [15–18], the presence of an extensive intraductal component [15], positive margins [19,20] or high-grade carcinoma [21]. However, the question remains whether giving an additional boost dose of radiotherapy can compensate for this higher risk of local recurrence. For example, there is a correlation between the molecular subtype of breast cancer and the ipsilateral breast recurrence rate, but the subtype does not seem to be predictive of the benefit of radiotherapy [22,23]. Randomised controlled trial data are crucial to help answer whether these prognostic factors are also predictive of the benefit of a boost such that we can select which patients will benefit most from a tumour bed boost.

The aforementioned EORTC Boost trial randomized 2657 patients and identified young age and high-grade carcinoma as risk factors for locoregional recurrence [15,16,23]. In addition, both for young age and high-grade carcinoma, the boost dose of 16 Gy significantly reduced the 10-year local relapse rate from 19.4% to 11.4% ($P = 0.0046$; HR 0.51) and from 18.9% to 8.6% ($P = 0.01$; HR, 0.42) respectively [21]. At 20 years' follow-up, the larger absolute benefit of a boost in younger age groups was confirmed [10]. With increasing age, the risk of developing severe fibrosis due to boost treatment increased, whilst the absolute benefit on local control decreased to about 3% in patients over 50 years old. In patients younger than 41 years the 20-year local recurrence risk was reduced from 36.0% to 24.4% and these patients were not at risk of increased severe fibrosis rates. The relative effect of invasive tumor grade on local control rapidly decreased in the first 5 years and eventually lost its significance [17]. However, the presence of ductal carcinoma in situ (DCIS) became prognostic for ipsilateral breast recurrence. In patients with DCIS, the boost dose reduced the 20-year risk of ipsilateral breast recurrence from 22% to 14% ($p < 0.001$, HR 0.47). This effect was even more pronounced in patients younger than 50 years (31% versus 15%, $p < 0.001$, HR 0.37) [17].

Delving deeper into which patients over the age of 50 could benefit from a boost, whilst the difference between the boost and no boost groups was small in the EORTC trial >50 years age group, the 95% confidence interval of the hazard ratio ranged from 0.43 to 1.14, suggesting a possible role for the boost in some, but not all, patients of over 50 years. The presence of DCIS did not seem to have an influence on the benefit of a boost in older patients (20-year incidence of ipsilateral breast recurrence 15% versus 14%, $P = 0.11$). Histological characteristics that are likely to be predictive of a benefit in patients over 50 years old include hormone receptor negativity and high grade (HR for all age groups with and without boost 0.43 (0.22–0.81) and 0.36 (0.18–0.70) respectively). In patients presenting with estrogen receptor negative, high grade tumours the ipsilateral breast recurrence risk was reduced from 31% to 5% (HR 0.23, $p = 0.01$) [17].

Another question is whether the boost can be omitted in younger patient subgroups with a lower risk of relapse. In the EORTC boost trial population as a whole, patients with low-grade estrogen receptor positive tumours did not seem to benefit from boost radiotherapy, even in the case of additional DCIS [17], but can we extend these findings to the younger patient groups knowing that, even in this favourable prognostic subgroup, patients younger than 40 years have a 15-year ipsilateral breast recurrence risk of 34%? This group requires particular thought given that the boost did not increase younger patients risk of fibrosis. It is likely that guidelines will continue to recommend boost in women of 40 years and under regardless of histopathology but it is important to bear in mind that, in the EORTC boost trial, systemic therapy was underused in comparison to current routine clinical practice. Indeed systemic therapy was only prescribed to node-positive patients (a minority of the study population) and consisted of tamoxifen for postmenopausal women and chemotherapy for premenopausal women. In the context of contemporary systemic regimens, the absolute benefit of the boost might therefore be smaller although the largest local control benefits in the EORTC boost trial were observed in the group receiving both systemic therapy and boost radiotherapy, suggesting complementarity of local and systemic treatments in higher-risk individuals.

Although close or positive margins are often used as a reason to boost, there is no strong evidence to support this pattern of practice. While positive margins have an adverse effect on outcome, it has been widely accepted that re-excision in case of 'no ink on tumour' is overtreatment since the distance of the negative margin is not correlated to local control [18–20]. In a meta-analysis of Houssami et al. the use of a radiotherapy boost did not seem to have an influence on outcome, either in the case of positive margins, or in the case of close margins ($p = 0.86$) [19]. In the EORTC boost trial the effect of the boost in patients with close/positive margins was similar to patients with free margins [17]. In the Budapest trial, however, the benefit of a boost seemed to be larger in case of close/positive margins. The boost dose reduced the 5-year local recurrence rate from 11.6% to 6.8% in case of negative margins and from 50.8% to 8.3% in case of close/positive margins [5]. Again, the patient numbers in the group with close/positive margins were very small and might have influenced the results. In general, margin status does not appear to be an independent risk factor to decide on boost radiotherapy.

So, conclusions to be drawn from the EORTC Boost trial are: 1) a boost dose can safely be omitted in patients older than 50 years with low-grade estrogen positive tumours; and 2) the benefit of boost radiotherapy cannot be ignored in patients of 50 years or younger with additional DCIS as well as in patients with high-grade hormone receptor negative tumours. In the grey zone are the low-grade estrogen receptor positive tumours in young patients and the high-grade estrogen receptor positive or low-grade hormone receptor negative tumours in older patients. In these subgroups, the risk of toxicity could be the deciding factor. The Young Boost Trial randomized 2421 cT1-2 N0-2a breast cancer patients of $\leq$50 years to a 16 Gy or 26 Gy boost [24]. Risk factors for worse cosmetic outcome were the use of a photon boost instead of an electron boost, a high boost dose, cosmesis at baseline, adjuvant chemotherapy and boost volume. In the current era, where patients are increasingly involved in their treatment, these findings may help us in the process of shared decision making and in evolving towards more individualized radiation treatment recommendations.

Turning now to patients who have received neo-adjuvant chemotherapy, there are no studies investigating the role of a boost in this setting. It seems obvious that patients with residual in-breast disease after chemotherapy could benefit from a boost dose, but is there a benefit from a tumour bed boost in patients with a complete in-breast response? A meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated a higher risk of local recurrence when using neo-adjuvant chemotherapy compared to adjuvant chemotherapy (21.4% versus 15.9%; $p = 0.0001$), suggesting a possible role for additional radiotherapy including a boost [25]. It should be noted however that this meta-analysis only included older trials (1983–2002) using predominantly non-taxane based chemotherapy. In those days MRI imaging and clip marking for tumour localization were not standard procedures and downstaging was the most important indication for neo-adjuvant chemotherapy. Nowadays, the indications for neoadjuvant systemic therapy have shifted to eradication of distant metastases and evaluation of response in triple negative and HER-2 positive tumours. In these higher-risk histologies, a boost dose might be considered even in the case of a complete pathological response albeit data demonstrate durable remission in HER2 positive patients treated with chemotherapy and dual antibody blockade [26,27]. Based on the available evidence, no firm conclusions can be drawn on boost strategy following complete pathological response to neo-adjuvant chemotherapy, but de-escalation of local treatment seems an option in these patients with an excellent prognosis. Kuerer et al. evaluated the omission of surgery in highly selected triple negative and Her2 positive breast cancer patients with a complete pathological response after neo-adjuvant chemotherapy. At a median follow-up of 26.4 months, no ipsilateral breast tumour recurrences were observed in 31 patients treated with radiotherapy alone

(NB this was whole-breast irradiation (40Gy in 15 fractions or 50Gy in 25 fractions) with a boost of 14Gy in 7 fractions to the original location of the primary) [28].

2.2. Is there a role for a boost in DCIS?

The role of a boost in patients with DCIS has always been controversial. Until recently, only retrospective studies had been available, showing conflicting results around the benefit of boost radiotherapy in this context. Now however we have the first results of the BIG 3–07/TROG 07.01 randomized trial [14]. In this study, 1608 patients with non-low risk DCIS were randomized between boost and no boost radiotherapy and between conventional fractionation and hypofractionation. Non-low risk DCIS was defined as at least one of the following characteristics: age <50 years, symptomatic presentation, palpable tumour, microscopic tumour size measuring ≥15 mm, multifocal disease, intermediate or high nuclear grade, central necrosis, comedo-histology, or a radial surgical margin of <10 mm. At 5 years of follow-up local control rates were higher in the group receiving a boost (97.1% versus 92.7%, $p < 0.001$), but at the expense of increased grade ≥2 breast pain (14% versus 10%, $p = 0.003$) and induration (14% versus 6%, $p < 0.001$). This is the first prospective randomized trial showing a possible role of a boost in non-low risk DCIS. There were no significant differences found in the effect of the tumour bed boost according to age, tumour size, nuclear grade, comedonecrosis, surgical margin width, or endocrine therapy use. However, the majority of patients (1397 of 1608 patients) did not receive endocrine therapy. Whether this small, but significant, gain in local control outweighs the increased risk of grade ≥2 side effects is a discussion to be had with each individual patient such that patients can reach an informed decision. For the future, gene expression profiling tests may help in this process of shared decision making albeit the health economic aspects of genomic testing in this setting need to be carefully evaluated.

3. How to boost?

3.1. Target volume definition

Having established that we should be more carefully targeting our use of boost radiotherapy in breast cancer patients, how should we treat those patients in whom we have decided a boost is required? First of all it is necessary to define (and then delineate) the target volume. In the adjuvant setting the primary cancer (or gross tumour volume) has been excised. As described earlier, the highest risk of relapse is thought to arise in the tissue proximal to the location of the original cancer. The clinical target volume (CTV) therefore needs to encompass the residual breast tissue that was closest to the primary tumour prior to its excision. In years past, when wide local excision of breast cancers more often involved making an incision close to the location of the cancer and excising a cylinder of tissue down to pectoral fascia, boost target volumes were related to scar position with the aim of adding a margin of 1–2 cm around where the cancer was thought to have been located but, even prior to the era of oncoplastic surgery, studies demonstrated that this scar-directed boost approach missed the clip-defined tumour bed in almost 70% of cases [29].

Subsequent studies investigated the use of gold seeds [30] or (a little more cheaply) titanium clips to mark the tumour bed (TB). A protocol [31] in which pairs of clips were placed immediately after wide local excision of the index cancer in the four radial margins of the TB, as well as at the deep and superficial margins has been demonstrated to be reliable and precise. This technique was used in the majority of patients treated within the IMPORT Low partial breast irradiation trial in which 5-year recurrence rates were around 1% in keeping with accurate localization of the highest risk part of the breast [32]. The same technique was applied within the IMPORT High boost trial (described in more detail below) and similarly associated with low local recurrence rates [see Table 1] [13]. It should be borne in mind that including the posterior clip, typically placed at the pectoral fascia and therefore at a varying distance from the back of the index lesion in the target volume, could potentially result in unnecessary large boost volumes in patients with a more anteriorly located primary cancer. This is especially an issue in prone treated patients where the posterior clip tends to stay close to the pectoral fascia, while the breast tissue falls forward due to gravity [33]. MRI has been shown to add little to the CT/clip-delineation method [34]. Investigators have also used pre-operative CT imaging to reconstruct GTV location and thereby inform CTV delineation [35]. In the Young Boost Trial, the boost CTV was defined as the rim of tissue around the original tumour. The location of the original tumour was defined using pre-operative clinical and imaging findings together with tumour bed clips, to which a 15 mm margin was added. Adding a margin of this magnitude leads to rather large boost volumes, perfectly reasonable in the context of partial breast irradiation, but perhaps overtreatment in case of whole-breast irradiation combined with boost radiotherapy. In light of increased rates of fibrosis and worse cosmetic outcome with larger boost volumes [36,37], taking the minimal surgical margin into account should at least be considered. Using asymmetrical margins around the clips based on the surgical margins in all directions, might even further reduce the boost volume, although the publication of Molina et al. teaches us to remain critical: a disorientation rate of >30% was observed when using stitches on 2 surfaces for specimen orientation [38]. In terms of being able to more accurately deliver a boost dose to a tumour, a pre-operative boost would seem to be ideal but this also remains untested in clinical trials. It is likely though that future studies will evaluate the combination of pre-operative boost radiotherapy with immunotherapy and targeted agents, for example in chemoresistant breast cancers, in which case the addition of imaging modalities such as MRI and PET-CT to standard CT may yet be helpful as has been the case for identifying smaller cancers prior to pre-operative partial breast irradiation [39].

Having defined the clinical target volume, for external beam radiotherapy techniques (the predominant technique in the EORTC Boost, Young Boost and several SIB trials), a margin needs to be added to account for daily changes in tumour bed position. In IMPORT High this was defined as clip-defined tumour bed plus 5 mm albeit using an extended no-action level verification protocol [40]. An Italian phase II trial [41] of simultaneous integrated boost (described further below) defined the boost PTV as the clip-defined tumour bed with a 10 mm margin. In this trial, patient position was verified daily using either CBCT or 2D-matching. Of course, the choice of CTV to PTV margin will ultimately depend on each centre's verification protocols but it is important to consider the ultimate irradiated volume (relating to earlier mentioned studies on fibrosis risk). Some protocols, for example, have placed a maximum limit on the volume of the boost planning target volume, for example <20% of the whole breast PTV [42].

3.1.1. Breast boost technique

In terms of radiotherapy technique [see Table 1 for a summary of these in the largest randomised controlled trials], 95% of patients in the EORTC Boost Trial [10] were treated with external beam techniques (n = 2393: electrons or photons) and 225 patients were treated with interstitial brachytherapy (described below). 16Gy/8# was delivered sequentially in all cases. In the Young Boost Trial, 2421 patients were randomised between a standard sequential 16Gy/8# boost versus a high dose boost in which 2Gy was given to the boost volume in each of weeks 1–5 of a 50Gy/25# regimen, followed sequentially by 8*2Gy to the boost volume. 34% of patients in the Young Boost trial were treated with a simultaneous integrated boost. In the standard dose arm, 28 fractions of 1.81 Gy were delivered to the whole breast with an additional 0.49 Gy/fraction to the boost volume (total 2.3 Gy/fraction to the boost volume) in the same 28 fractions. In the high dose arm, 31 fractions of 1.66 Gy were delivered to the whole breast with an additional 0.72 Gy/fraction to the boost volume (total of 2.38 Gy/fraction to the boost

volume) in the same 31 fractions. Risk factors for fibrosis included use of photons (described as "oblique wedged photon beams") rather than electrons, higher dose, larger boost volume, poor pre-RT cosmesis and use of adjuvant chemo. IMPORT High used only conformal photon boosts, a pre-trial QA study having demonstrated that electron boosts frequently underdosed the tumour bed. CTV to PTV margin was 5 mm in order to avoid boost volumes becoming too large and thereby increasing the risk of fibrosis. Both sequential and simultaneous integrated boosts were delivered using either a forward-or inverse planned IMRT.

Interstitial brachytherapy has the advantage of not requiring a CTV to PTV margin such that a smaller volume of breast tissues is irradiated to a higher dose. ESTRO-ACROP guidelines published in 2018 recommend 3-dimensional planning ideally using CT to define the tumour bed using tumour bed clips and therefore to guide catheter placement [43]. Detailed guidelines for target volume delineation (with specific recommendations based on whether the excision cavity is closed or open) recommend an optimal value of safety margin of around 2 cm (including the resection margin and the safety margin around the edge of the excision cavity) [44,45]. In the EORTC Boost Trial, a 15Gy boost (equivalent to a 16Gy external beam dose) was delivered using an ^{192}Iridium implant at a dose rate of 0.5Gy per day. The dose was specified at the centre of tumour excision area. In the Budapest boost study (n = 207), 52 patients received a high dose rate (HDR) boost of 12–14.25 Gy [5]. At a median follow-up of 5.3 years, the crude rate of local recurrence was 5.7% in the boost arm and 15.5% in the non-boost arm. There was no significant difference between local recurrence rates in those treated with electron versus brachytherapy techniques. There were more grade 2–3 side-effects in the boost arm (17% versus 8%, p = 0.03) but no difference in the rates of excellent/good cosmesis (86% boost versus 91% no boost, p = 0.14).

In relation to intra-operative radiotherapy (IORT), an International Society of IORT pooled analysis has demonstrated in 1109 patients that, at a median follow-up of 72 months, intra-operative electron radiotherapy (IOERT) is associated with a 99% local control rate. In this analysis the median IOERT boost dose was 10 Gy followed by 50–54 Gy whole breast radiotherapy delivered in 1.2 Gy–2 Gy fractions. More recently, Fastner et al. reported outcomes of a prospective single-arm trial (HIOB) of 11.1 Gy IOERT followed by 40.05 Gy in 15 fractions to the whole breast [46,47]. 85% of patients at T1 primary tumours and median IOERT tube diameter was 6 cm. In 583 patients at median follow-up of 45 months (range 0–74 months), LENT-SOMA ratings for late reactions were G0-1 in 93% of patients. In contrast, Leonardi et al. reported 10-year outcomes in 481 patients ≤48 years with T1-2N0-1 breast cancers treated with a 12Gy IOERT boost followed by adjuvant whole breast radiotherapy 13 × 2.85 Gy [48]. Median tumour size was 1.5 cm and median IOERT applicator size was 4 cm. The 10-year cumulative incidence of local relapse was 4.1% but moderate/severe fibrosis was reported in 41% patients. The authors attribute the higher toxicity rate to a possible combination of the higher boost dose (EQD2 cumulative boost dose of 78 Gy for the Leonardi study versus 71 Gy for the HIOB trial), surgical techniques involving more mobilisation of glandular breast tissue and optional use of shielding discs. Intra-operative photon radiotherapy is currently under investigation in the TARGIT-B trial which randomises patients at higher risk of local recurrence between a 20Gy low energy (up to 50 kV) x-ray boost versus an external beam photon boost delivered according to local practice [49]. The primary endpoint is local tumour control. It should be noted however that, in a small substudy of TARGIT-A, the risk of long-term firmness in the breast in patients who were found following histopathological evaluation of the surgical excision specimen to need external beam whole breast radiotherapy following their IORT was 37% [50].

To summarise, there are published data underpinning the use of photons, electrons and interstitial brachytherapy as techniques for breast boost irradiation (with choice of technique dependent on local expertise, particularly in the case of brachytherapy). In relation to intra-operative techniques, the dose and technique of an IORT boost should be considered carefully in order to avoid unacceptable risks of long-term fibrosis.

3.1.2. Dose-fractionation

With regards to dose-fractionation, sequential electron boosts have most often been delivered in the literature using 2Gy per fraction schedules of between 10 Gy and 16 Gy in 5–8 fractions. 16 Gy in 8 consecutive daily fractions was the dose used in the largest (n = 5318) boost versus no boost RCT demonstrating the local control advantage of a boost in women of young age and/or with high grade disease [10]. Neither the Young Boost trial nor the IMPORT High showed any improvement in local control using boost doses higher than 16 Gy/8# or equivalent [see Table 1] [13,11,12]. Following demonstration of the efficacy and reduced toxicity of moderately hypofractionated whole breast radiotherapy schedules, boosts have also become increasingly hypofractionated in clinical practice. The Lyon boost trial tested 10 Gy/4# daily with a 3.6% local relapse rate at 10 years [4]. In the Budapest boost versus no boost trial, Polgar et al. treated half their boost patients (n = 52) with a 16 Gy/8# electron boost and half (n = 52) with a hypofractionated boost of 12 Gy in 3# HDR brachytherapy boost) [5]. There was no difference in local control (5-year local control 94% for 16 Gy/8# versus 91% for 12 Gy/3#, p = 0.74). Neither was there a difference in long-term toxicity between those treated with electrons (16Gy/8#, 83% patients rated cosmesis as excellent/good)) versus HDR (12Gy/3#, 89% patients rated cosmesis excellent/good, p = 0.29) albeit numbers are likely too small to be able to draw firm conclusions. In the IMPORT High trial, the test arms included hypofractionated simultaneous integrated boosts [see Table 1 for dose-fractionations] [13]. There was no difference in the risk of local recurrence between those treated with 40Gy/15# to the whole breast followed by a 16Gy/8# boost versus those treated with a simultaneous integrated 3.2Gy × 15# boost. To summarise, there do not appear to be any data suggesting that a hypofractionated equivalent of 16Gy/8# would be disadvantageous in terms of local control or toxicity with both ASTRO and RCR guidelines permitting hypofractionated boosts [51,24]. Where interstitial HDR brachytherapy is used, ESTRO-ACROP guidelines recommend a biologically equivalent dose in the range of 10–20Gy delivered in 1–4 fractions (such as 2*4–6Gy or 3*3–5 Gy scheduled 2 times per day), with an interval between fractions of at least 6 h, and a total treatment time of 1–2 days, or a single fraction of 7–10 Gy, depending on the desired total EQD2 [43]. For pulsed dose rate brachytherapy, these same guidelines recommend pulses of 0.5–0.8 Gy to a total dose of 10–20 Gy scheduled hourly, 24 h per day with a total treatment time of 1–2 days.

More recently the use of simultaneous integrated photon boosts (SIB) has been increasing. This has been facilitated by deployment of more advanced techniques in breast radiotherapy including intensity-modulated and image-guided radiotherapy. Franceschini et al. treated 450 patients in a prospective cohort study with 40.5 Gy/15# whole breast and a 48 Gy/15# SIB. At a median follow-up of 6 years, the risk of local recurrence was 1.1%. Cosmesis was excellent or good in 99% [41]. Osa et al. (using predominantly a prone technique) treated 404 patients in a prospective phase II trial using the same dose-fractionation regimen as Franceschini (a phase III trial is ongoing) [52]. At a median follow-up of 5yrs, the local recurrence rate was 0.8%. 82% of patients reported their 5-year cosmetic outcome as being excellent/good. Pfaffendorf et al. reported outcomes in 300 patients enrolled in two phase II trials of 40 Gy/16# with a 48 Gy/16# SIB [42]. At a median follow-up of 5 years, the local recurrence rate was 1% with 64% of patients reporting no late toxixity. Only 2 of 300 patients reported G3 toxicity (telangiectasia and breast swelling respectively). Van Hulle et al. [53] recently published two-year results on 150 evaluable patients from their randomized controlled trial comparing hypofractionated whole-breast radiotherapy with a sequential boost to a 15- fraction regimen of 40.05 Gy to the whole breast and a SIB of 46.8 Gy (negative margin) or 49.95 Gy (positive margin) to the tumor bed. There was no grade 3 toxicity. No significant differences were observed between the two treatment arms in

terms of late toxicity and cosmetic outcome. Recently, 5-year data from the IMPORT HIGH-trial were presented. This is a 3-arm randomized controlled trial with 2617 patients comparing 40.05 Gy in 15 fractions followed by a sequential boost of 8 × 2 Gy to two different 15-fraction SIB regimens [13]. Both test arms used a reduced dose of 36 Gy to the uninvolved breast and delivered 40 Gy only to a partial breast volume (clip-defined tumour bed plus 15 mm to CTV and 10 mm to PTV). The SIB doses (prescribed to the clip-defined tumour bed plus 5 mm) were 48 Gy and 53 Gy respectively. At 74-months median follow-up the five-year rate of ipsilateral breast tumour recurrence was 1.9% for the sequential arm, 2.0% for the 48 Gy arm and 3.2% for the 53 Gy arm. The cumulative five-year incidence of clinician-reported moderate/marked breast induration was 12% for the control arm, 11% for the 48 Gy SIB arm and 16% for the 53 Gy SIB arm. Overall, there are now substantial data to support the use of a 48 Gy/15# SIB. Technical approaches used in the SIB trials have predominantly involved supine forward and inverse planned intensity-modulated (IMRT), more recently using deep inspiratory breath-hold for left-breast-affected patients [13,54]. A prone position has also been used [53]. Hybrid IMRT or volumetric-modulated arc therapy (VMAT) techniques in which the majority of the radiation dose is delivered tangentially with only the SIB dose delivered via non-tangential fields can potentially reduce the low dose bath compared to full IMRT/VMAT.

Next steps in evaluation of the breast boost include evaluation of whether or not a SIB can be delivered in 5 fractions. Van Hulle et al. randomised 200 patients between 40 Gy/15# with a simultaneous integrated boost of 46.8 Gy/15# versus 28.5 Gy in 5 fractions with a SIB of 31 Gy/5#, the overall treatment time being 10–12 days [54]. Physician-assessed toxicity was lower (significantly less breast pain, fatigue, breast oedema and dermatitis in the 5-fraction group). In addition health-related quality of life was better in the 5-fraction group. Long-term toxicity data are awaited. A five-fraction SIB is also being investigated in the Indian HYPORT Study which randomises patients to 40 Gy/15# versus 26 Gy/5# with those patients requiring SIB being treated to 48 Gy/15# and 32 Gy/5# respectively. Acute toxicity data in 271 patients treated so far have reported grade 3 radiation dermatitis in 3 patients none of whom were treated with a SIB [55]. No other G3 or higher toxicities were reported. This trial continues to accrue and longer-term local control and toxicity data are awaited but ultimately dose-fractionation of boost is another dimension in which it is likely that less will be more.

Standardising global practices remains challenging given the array of available technical approaches studied in a variety of clinical trials. Through international consensus guidelines and defined inclusion criteria & radiotherapy quality assurance approaches in ongoing and forthcoming trials, we can continue to improve the quality and consistency of boost practices in breast radiotherapy.

4. Conclusions

Delivery of additional dose to the region of breast tissue proximal to the original breast primary has a sound clinicopathological basis. In the context of falling local relapse rates, and in the absence of a survival advantage, the proportion of patients requiring a tumour bed boost should also be falling (with key suggested eligibility criteria including young age, high grade and triple negative phenotype). Where a boost is delivered, the target volume and treatment burden should be minimised for example using clip-defined simultaneous integrated photon boosts or brachytherapy, ideally delivering treatment over no more than 3–4 weeks to minimise the treatment burden for the patient and for health economies.

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.

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