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Fractionation Approaches in Whole Breast RT

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Abstract

Purpose of Review To review the current approaches to fractionation from phase III prospective randomized trials for post-lumpectomy whole breast radiation therapy (WBRT) for early-stage breast cancer.

Recent Findings Moderate hypofractionation (M-WBRT) given Monday through Friday over 3–4 weeks is now standard practice for almost all patients needing postlumpectomy WBRT. The use of M-WBRT is being expanded to include regional node irradiation (RNI) and may be further shortened by a tumor bed boost that is concurrent rather than sequential to avoid extra days of treatment. And for selected patients, there is now an option for ultra-hypofractionation (U-WBRT) that further shortens WBRT to as few as 5 treatments in 1 week.

Summary When WBRT is indicated after lumpectomy for early-stage breast cancer, moderate hypofractionation over 3 weeks is the preferred radiation schedule for most patients. Select patients are eligible for a 1-week schedule using ultra-hypofractionation.

Keywords Radiation therapy · Breast cancer lumpectomy radiation · Whole breast irradiation · Hypofractionated radiotherapy · Tumor bed boost

Introduction

The combination of breast-conservation surgery (BCS) and whole breast radiation therapy (WBRT) has been the worldwide standard alternative to mastectomy for early-stage invasive breast cancer for over 40 years. Although relatively static in its nature for the first three decades, WBRT has experienced a golden age of progress in many aspects in only the past decade.

The eligibility for WBRT has become more inclusive than ever before. Improvements in screening and multidisciplinary management of breast cancer have made BCS and WBRT available to almost all patients with early stage. Even tumors of larger size or multiple foci can be amenable to BCS today with or without neoadjuvant chemotherapy. And after BCS, WBRT is open to the most inclusive range of patient and tumor characteristics compared to partial breast radiation or omission of radiation which are very restrictive in their eligibility. Patients with almost any age, histology, receptor subtype, node status, or systemic therapy are eligible for postlumpectomy WBRT.

The early experiences with BCS and WBRT in the 1980s–1990s had 10-year rates of ipsilateral breast tumor recurrence (IBTR) on the order of 15%, and even higher in certain high-risk subgroups. WBRT in that era was assumed to have inferior local control to mastectomy even if survival was equal. But improved multidisciplinary selection and care in the past decade including better imaging, surgical localization techniques, pathologic margin assessment, systemic therapy, and genetic testing have all resulted in IBTR outcomes after WBRT of 2–3% at 10 years. These results with BCS and WBRT today now equal the best comparable outcomes with mastectomy.

And the past decade has welcomed major technological advances in planning and delivery of WBRT. Skin dermatitis and other acute effects have been reduced by improvements in 3D planning and dose delivery that result in more uniform dose homogeneity that avoids hot spots. Prone positioning improves set-up and toxicity for large and pendulous breast size. Modern linear accelerators can deliver complex plans in a matter of minutes on the table for the patient. And the dose to heart and lung is lower than ever before with the use of prone positioning, deep inspiration breath holding,

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or intensity-modulated radiation therapy when needed. Prospective data for WBRT since the 2000s now shows late risks for serious cardiac or pulmonary toxicities under 1–2%.

But the focus of this review is how WBRT in the past decade has been radically transformed by improvements in the understanding of the biology of fractionation. For 30 years from the 1980s until the mid-2010s, WBRT remained fixed in the USA at Monday through Friday for 6–7 weeks. The use of hypofractionation, or a fewer number of fractions with a higher dose per fraction compared to conventional 1.8–2-Gy fraction sizes, has significantly reduced the length of treatment for WBRT. The past 10 years have seen numerous large, prospective randomized phase III clinical trials of whole breast hypofractionated radiation with long-term results. These trials of moderate hypofractionation (M-WBRT) have made a treatment length for WBRT of 3–4 weeks standard for most patients. And for some patients, there is also data that ultra-hypofractionation (U-WBRT) in shorter courses of 5 weekly fractions or consecutively in 1 week is safe and effective.

This review will examine the current fractionation approaches for WBRT with an emphasis on the phase III randomized trials and major international consensus panel recommendations. While M-WBRT is already open to most patients with early-stage breast cancer, the expansion of its use for patients with need of simultaneous regional node irradiation (RNI) will be discussed. Because most of these hypofractionation trials used a conventional sequential tumor bed boost after WBRT, that adds an additional 4–5 days of treatment thus negating some of the overall benefit in time for hypofractionation. This review will also discuss the latest phase III data on how a concurrent tumor bed boost can be combined with M-WBRT to avoid extending treatment length. Lastly, this review will present the prospective phase III data for U-WBRT and how this is rapidly increasing in use in many countries particularly accelerated by the COVID pandemic.

Moderate Hypofractionated Whole Breast Radiation Therapy

Hypofractionation is the use of radiation using larger than a conventional 1.8–2 Gy fraction size, and generally also means a course of radiation that is delivered in a fewer total number of fractions in a shorter period of time than conventional fractionation. In the 1980s, when postlumpectomy WBRT first became a standard alternative to mastectomy, the prospective phase III trials used predominately conventional fractionation given Monday through Friday over 6–7 weeks. Although this remained the standard in the USA for over 30 years through the 2010s, internationally during this time there was research and development of alternative hypofractionation regimens for WBRT that developed from retrospective reports to prospective clinical trials. There are now numerous published international prospective randomized phase III trials of M-WBRT with long-term results and large numbers of patients (Table 1 and Fig. 1). These robust results have made M-WBRT the current standard of practice worldwide including now in the USA. M-WBRT could actually now be appropriately considered the new "conventional" fractionation in breast cancer, but to avoid confusion, that term "conventional" remains most commonly associated with ≤ 2-Gy fraction size.

The phase III trials of M-WBRT in Table 1 have uniformly demonstrated both non-inferior disease-specific cancer outcomes but also no difference in breast-related and other toxicity outcomes by fractionation. All of the phase III trials have shown M-WBRT with non-inferior long-term local control, disease-free, and overall survival outcomes compared to conventional fractionation. Even more, consistent with the trend of improving local control in the past decade with BCS and WBRT in general, the phase III trials started in the past 10–15 years have shown ipsilateral breast tumor recurrence (IBTR) of ≤ 3% from 7 to 10 years after treatment. The acute and late toxicities of WBRT have been equal with M-WBRT compared to conventional fractionation as well in these trials. There have been equal or better acute and long-term breast-related effects of radiation including dermatitis, breast pain, breast edema, or skin telangiectasias with M-WBRT. Rare but serious late toxicities including heart, lung, and rib have been equally rare regardless of fractionation. And M-WBRT has also been shown to be equal or more often better in these trials for long-term global cosmetic appearance of the treated breast and patient satisfaction. These results have been shown regardless of subgroups based on age or other tumor characteristics.

In light of this extensive body of phase III data, consensus guidelines in the USA are very clear that M-WBRT should be standard practice for most patients needing postlumpectomy WBRT. An American Society for Radiation Oncology (ASTRO) task force recommended M-WBRT of 40–42.5 Gy in 15–16 fractions in most cases when the breast with or without low axilla was being treated [1]. This recommendation for M-WBRT was inclusive of any tumor size, tumor grade, margin status, hormone receptor status, HER2 receptor status or concurrent HER2-targeted therapy, presence of ductal carcinoma in situ, or any sequential (not concurrent) chemotherapy. In addition, the task force recommended that patients of all ages be eligible for M-WBRT, but with a special provision that individualized decision-making be given to patients < 40 years. Current National Comprehensive Cancer Network (NCCN) guidelines also recommend M-WBRT as the preferred fractionation given with 40–42.5 Gy in 15–16 fractions, and conventional fractionation of 45–50.4 Gy in 25–28 fractions only in cases needing

Table 1 Prospective randomized phase III trials of BCS and WBRT using hypofractionation and their use of a boost, use of regional node irradiation, and outcomes of ipsilateral breast tumor recurrence (see Fig. 1 for abbreviations)

Trial	Years conducted	Patients (number)	Whole breast fractionation (Gy/fractions)	Boost timing	Boost used	Boost fractionation (Gy/fractions)	RNI used	10-year IBTR[a] (%)	Reference
Moderate hypofractionated WBRT									
RMH/GOC	1986–1998	1410	50/25 42.9/13 39/13	Sequential only	74%	14/7	21%	12% 10% 15%	(36)
OCOG	1993–1996	1234	50/25 42.5/16	N/A	N/A	N/A	None	7% 6%	(37)
START A	1998–2002	2236	50/25 41.6/13 39/13	Sequential only	61%	10/5	14%	7% 6% 8%	(9)
START B	1999–2001	2215	50/25 40/15	Sequential only	43%	10/5	7%	5% 4%	(9)
DBCG HYPO	2009–2014	1854	50/25 40/15	Sequential only	23%	10/5	None	3% 3% (9-year)	(19)
IMPORT HIGH	2009–2015	2617	40/15 36–40/15 36–40/15	Sequential	100%	16/8 8/15 13/15	Allowed	1.9% 2.0% 3.2% (5-year)	(24)
CAMS	2010–2015	734	50/25 43.5/15	Sequential only	100%	10/5 vs. 8.7/3	4% 3%	2% 1% (5-year)	(38)
MDACC	2011–2014	287	50/25 42.56/16	Sequential only	99%	10/5 or 14/7 vs. 10/4 or 12.5/5	None	1% 1% (3-year)	(18)
NRG RTOG 1005	2011–2014	2354	50/25 or 42.7/16 40/15	Sequential vs. concurrent	100%	12/6 or 14/7 vs. 8/15 concurrent	None	2% 3% (7-year)	(23)
Ultra-hypofractionated WBRT									
UK FAST	2004–2007	915	50/25 30/5 28.5/5	N/A	N/A	N/A	None	1% 1% 1%	(30)
UK FAST-Forward	2011–2014	4096	40/15 27/5 26/5	Sequential only	25%	10/5 or 16/8	None	2% 2% 1% (5-year)	(31)

[a]Numbers rounded to nearest percentage

RNI (see below) or other unspecified selected cases [2]. NCCN did not give a specific cautionary note for M-WBRT by age or other clinical or pathologic factors. Many other consensus statements worldwide also have recommended M-WBRT in almost all cases of postlumpectomy WBRT [3–8].

The major exclusionary factor from M-WBRT, at least in the USA based on ASTRO and NCCN guidelines, has been using it in combination with RNI encompassing more than the low axilla – namely when there are added supraclavicular or internal mammary fields. The rationale for special caution in these cases during the 2010s may have been a special concern for added risks for serious cardiac, pulmonary, or brachial plexus late toxicity from RNI. But the 2016 UK Consensus Statement for postoperative radiotherapy for breast cancer and the European Society for Radiotherapy and Oncology (ESTRO) Advisory Committee in Radiation Oncology 2022 Practice Consensus Statement have recommended M-WBRT for any patient even with concurrent RNI [3, 4]. Although a relatively small subgroup of patients were treated with RNI in the phase III trials of H-WBRT (Table 1), the same biologic rationale for why M-WBRT results in the same or better breast outcomes as conventional fractionation also should apply to RNI. The estimated alpha–beta value of 3.5 for the breast, a radiobiologic measure of fractionation sensitivity of a tissue, from the START trials is comparable to a value of 3 routinely used for calculating risk to late-responding tissue such as heart

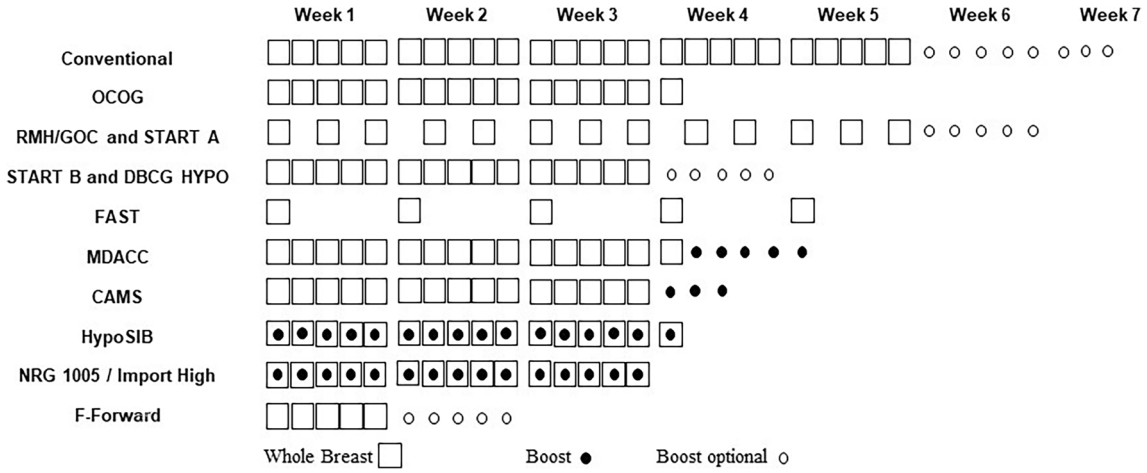

Fig. 1 Conventional, moderate, and ultra-hypofractionated whole breast radiation therapy regimens with or without sequential and concurrent boost used in phase III prospective trials. CAMS, Chinese Academy of Medical Sciences; DBCG, Danish Breast Cancer Group; IMPORT, Intensity-Modulated Partial Organ Radiotherapy; MDACC, MD Anderson Cancer Center; NRG, NRG Oncology; OCOG, Ontario Clinical Oncology Group; RMH/GOC, Royal Marsden Hospital/Gloucestershire Oncology Centre; RTOG, Radiation Therapy Oncology Group; START, Standardisation of Radiotherapy

or nerve [9] And the reports from subsets treated with RNI on the phase III trials of M-WBRT particularly the START trials did not exhibit added toxicity [10]. Nor has there been evidence of added toxicity in other phase II trials such as the Rutgers prospective trial of 3.33 Gy × 11 in which 11% of patients also had RNI [11]. There are many other long-term results from moderate hypofractionation for RNI from post-mastectomy trials and prospective WBRT databases [12–14]. There is likely going to be a parallel very slow adoption of M-WBRT and RNI in the USA comparable to the very slow adoption of M-WBRT in the USA during the 2010s for the breast alone [15]. Causes may be resistance to change, the negative reinforcement against hypofractionation from payment in the USA by the number of fractions, reluctance to adopt phase III data from other countries, or a slow response by organizations like ASTRO and NCCN to change their guidelines. However, in 2020 at the outset of the worldwide COVID pandemic, international guidelines recommended M-WBFRT for all cases of breast or chest wall even needing nodal radiation 40 Gy in 15 fractions [16]. Given the already widespread worldwide adoption, the resistance in the USA to moderate hypofractionation for RNI should give way more rapidly than did the resistance for the whole breast alone. The publication of the favorable phase II results of RNI in the setting of mastectomy and reconstruction, and the subsequent pending phase III RT CHARM Alliance trial (NCT03414970) if non-inferior, should even further accelerate the process of adopting M-WBRT and RNI in the USA [17].

Aside from RNI discussed above, there are relatively few remaining contraindications to M-WBRT. Because of the possible increased soft tissue and cosmetic effects and lack of data, concurrent administration of chemotherapy is not recommended. While in the past women with large breast sizes were not recommended for M-WBRT, now all sizes of women are potentially eligible. The ASTRO task force recommended rather than restrictions on any specific breast size, that the radiation dose homogeneity be a priority in planning such that the volume of breast tissue receiving 105% of the prescription dose be minimized. There is also phase III data on large breast size from the Danish HYPO trial and MD Anderson Cancer Center trials that there is a lower risk of adverse cosmetic outcome with large-breasted women and M-WBRT compared to smaller breasted women [18, 19]. Current methods of radiation treatment planning such as 3D forward planning, prone positioning, or intensity-modulated radiation therapy can optimize the dose homogeneity for most patients even with large or pendulous breast size so that they remain eligible for M-WBRT. A radiation tumor bed boost is also not a contraindication to M-WBRT. In the meta-analysis of the UK START trials, there was a significant reduction in the occurrence of moderate to marked tissue effects comparing H-WBRT to conventional fractionation both in patients treated with (HR 0.86) or without (HR 0.80) a tumor bed boost [9]. And in the MD Anderson randomized trial comparing H-WBRT to conventional fractionation, where there was a tumor bed boost in both trial arms, H-WBRT remained associated with improved dermatitis, pruritis, breast pain, fatigue, and non-inferior patient-reported cosmetic outcome at 3 years compared to conventional fractionation [18].

Moderate H-WBRT and Concurrent Tumor Bed Boost

A radiation boost in the setting of WBRT refers to an additional dose focused on and around the site of the lumpectomy bed. A tumor bed boost has been shown in a meta-analysis of randomized prospective trials to reduce the risk for IBTR compared to WBRT alone by 36% [20]. NCCN guidelines recommend a tumor bed boost in patients at higher risk for recurrence such as age < 50 years, high-grade disease, or a focally positive margin [2]. In a subgroup analysis of the largest randomized prospective trial of WBRT comparing boost to no boost, there was an increased risk for IBTR that was reduced by the boost for high grade (18.9–8.6%, $p = 0.01$) and young age < 50 years (19.4–11.4%, $p = 0.0046$) [21]. However, prospective evidence for a boost for positive margins is relatively lacking in comparison and is mainly based on retrospective evidence [21, 22]. An ASTRO task force recommended a tumor bed boost for higher risk features of age ≤ 50 years with any grade, age 51–70 years with high grade, or a positive resection margin [1]. It recommended omitting a tumor bed boost in low-risk patients including age > 70 years with low or intermediate grade and widely negative (≥ 2 mm) margins. For intermediate-risk patients fitting neither of these low- or high-risk definitions, they recommended shared decision-making that takes into account patient preferences and a physician assessment of the boost benefit versus risk.

The decision to use a tumor bed boost should be independent of the fractionation used for the whole breast. A boost can be given with M-WBRT just as with conventionally fractionated WBRT. However, a boost traditionally for decades has been given sequentially after WBRT. A sequential boost was used in the original phase III trials of lumpectomy and WBRT versus mastectomy, the phase III trials of WBRT and boost versus no boost, the phase III trials of M-WBRT versus conventionally fractionated WBRT, and the one phase III trial of U-WBRT versus M-WBRT (Table 1 and Fig. 1). The boost fractionation was historically 10–16 Gy in 5–8 fractions using conventional fraction size, but a boost can be given with H-WBRT in 10–12.5 Gy in 4–5 fractions as well [1]. However, this use of a sequential boost will add an additional 1–1½ weeks to the WBRT, and thus negate a large portion of the benefit of shortening overall treatment length by hypofractionation in the first place. M-WBRT has reduced treatment from a conventional 25–28 fractions to 15–16 fractions—a 10–13 fraction savings in days. If a 4–8 fraction boost were to be added sequentially to M-WBRT, then up to 50% of this 2–2½ week savings from M-WBRT is eliminated. A concurrent boost with M-WBRT, where the tumor bed boost is incorporated daily, would avoid prolonging the number of treatments, adding cost, or inconvenience from the boost to the patient.

There is now phase III data that M-WBRT with a concurrent boost is non-inferior to M-WBRT or conventionally fractionated WBRT with a sequential boost. NRG Oncology conducted a phase III randomized trial (NRG/RTOG 1005) of M-WBRT with a concurrent boost versus a control arm of conventional WBRT or M-WBRT with a sequential boost (Table 1) [23]. The control arm (1124 patients) was 4½–6½ weeks using either WBRT 50 Gy in 25 fractions or M-WBRT 42.7 Gy in 16 fractions followed by a sequential boost of 12–14 Gy. The investigational arm (1138 patients) was 3 weeks with M-WBRT dose-fractionation of 40 Gy in 15 fractions of 2.67 Gy per fraction, and a concurrent tumor bed boost of 3.2 Gy per fraction to give a total to the lumpectomy bed of 48 Gy in the same 15 fractions. The eligibility was broad to include patients at higher than average risk for IBTR due to one or more factors where there would be general consensus that a boost was indicated—age < 50 years, node positive, lymphovascular space invasion, presence of an extensive in situ ductal component (EIC), close resection margins, focally positive resection margins, non-hormone-sensitive breast cancer, and neoadjuvant chemotherapy. Any combination of 3D (photon or electron) or IMRT techniques for the whole breast and concurrent boost were permitted. With a median follow-up of 7.4 years, the 7-year IBTR was 2.6% (1.9–3.5 90% confidence interval (CI)) versus 2.2% (1.5–3.0 90% CI) and non-inferior. There was also non-inferiority for the 3-year change in baseline of the mean physician-assessed and patient-assessed cosmetic outcomes with M-WBRT and concurrent boost. Lastly, there was no significant difference in grade ≥ 3 toxicity (3.5% vs. 3.3%, $p = 0.79$).

The IMPORT (Intensity Modulation and Partial Organ) High trial in the United Kingdom was a three-arm trial combining M-WBRT with a sequential boost versus 2 different dose levels of concurrent boost [24]. The controls were treated with M-WBRT 40 Gy in 15 fractions with a sequential boost of 16 Gy in 8 fractions over 4 ½ weeks. The two investigational arms used M-WBRT to 36-Gy whole breast and 40-Gy involved quadrant in 15 fractions, with a concurrent tumor bed boost to 48 Gy or 53 Gy. There was non-inferiority with the 48-Gy concurrent boost in both 5-year IBTR and the prevalence of adverse breast appearance effects. However, there was no advantage to the dose-escalated 53-Gy boost in IBTR, and even more it was associated with greater breast cosmetic changes compared to the 48 Gy boost level. Two other phase III trials of M-WBRT and concurrent boost versus sequential are pending (NCT02474641, NCT01973634). The IMRT-MC2 Trial also showed non-inferiority of WBRT with concurrent boost versus sequential boost, but this was not testing hypofractionation as both arms used conventionally fractionated WBRT 50.4 Gy in 28

fractions [25]. Attempting to shorten length of treatment for M-WBRT and boost even further, a phase III trial is comparing M-WBRT (40 Gy in 15 fractions) with concurrent boost (48 Gy) in 3 weeks versus M-WBRT (32 Gy in 10 fractions) and concurrent boost (42 Gy) in 2 weeks (NCT04175210).

The main contraindication to a concurrent boost is when a lumpectomy bed at initial simulation is too large in comparison to the size of the whole breast. The NRG/RTOG 1005 trial of concurrent versus sequential boost included dose limits on how much of the whole breast could receive the boost dose (approximately ≤ 30%). The IMPORT HIGH trial recommended that the tumor bed CTV be ≤ 5% of the whole breast PTV for similar reasons of problems generating acceptable plans with very large seromas. In some cases of a very large lumpectomy bed, a boost may not be possible altogether. But in many cases, a sequential boost may be possible if a large seroma present at initial simulation can reduce in size with time so that the tumor bed-to-breast size ratio improves. With long periods of time, seromas will decrease or resolve altogether. For example, in a subset analysis of the IMPORT HIGH trial, it was noted that the prevalence of seroma was lower after systemic chemotherapy that takes months (10% vs. 29%) [26]. However, seromas and particularly large seromas at simulation do rapidly improve even during the short interval of 3–5 weeks between initial simulation and the first day of the boost [27, 28]. So for the patient with a large seroma at simulation, instead of concurrent boost, a delay to boost planning during week 3 of a course of M-WBRT may make a sequential boost still possible.

Ultra-hypofractionated Whole Breast Radiation Therapy

The success of the Canadian and START phase III trials of M-WBRT in matching IBTR and late toxicity of conventional radiation validated the radiobiologic model of fractionation sensitivity for the breast with an estimated alpha–beta value of 3.5. In the UK, this new standard WBRT 15-fraction regimen was felt "unlikely to represent the useful limits of hypofractionation for whole breast radiotherapy" [29]. This led to the development of 2 more phase III trials of U-WBRT that further shortened the number of fractions needed for treatment (Table 1). Similar to the adjustments made going from conventional WBRT to M-WBRT, the fraction size was raised even more while commensurately the total dose was adjusted downward.

The FAST trial tested conventional WBRT of 50 Gy in 25 fractions over 5 weeks (standard for WBRT in the UK at the trial onset) against U-WBRT 28.5 or 30 Gy in only 5 fractions once a week (keeping the treatment duration also 5 weeks) [30] Women ≥ 50 with tumor size < 3 cm and pN0 were eligible. There was no mastectomy, RNI, or tumor bed boost. After 9.9 years of median follow-up, there were no significant differences in 10-year IBTR of approximately 1%. The breast normal tissue effects and change in photographic appearance were not significantly different between 28.5 Gy in 5 fractions compared to 50 Gy in 25 fractions, but there were more moderate/marked negative effects in the 30-Gy arm. The FAST-Forward trial tested conventional WBRT of 40 Gy in 15 fractions in 3 weeks (standard for WBRT in the UK at the trial onset) against U-WBRT 26 Gy or 27 Gy in only 5 fractions in 1 week [31]. The eligibility was even more inclusive than FAST for T1-3, N0-1, lumpectomy (93%), or mastectomy with or without reconstruction (7%), and tumor bed boost (25%) but no RNI. Median age was 60–61 with approximately 15% < 50. After a median follow-up of 6 years, the 5-year IBTR was non-inferior for both U-WBRT regimens compared to M-WBRT of approximately 2%. Patient and photographic assessments showed higher normal tissue effect risk for 27 Gy versus 40 Gy but not for 26 Gy versus 40 Gy, although overall incidence of moderate or marked tissue effects in the breast (or chest wall) was relatively low at 10% for 40 Gy, 12% for 26 Gy, and 15% for 27 Gy. There is little data on the added late effects of a tumor bed boost with U-WBRT. Although any added negative effects of the boost were not specifically noted, if only 1 extra Gy with U-WBRT (27 Gy vs. 26 Gy) could increase late effects to a significant degree, then a tumor bed boost of 10–16 Gy should be used very cautiously if at all.

The large phase III trial evidence for M-WBRT resulted in a fairly slow change in practice from 2010 to 2020. However, the comparatively smaller phase III trial evidence for U-WBRT has been associated with a very rapid change in practice from 2020 to present. The major difference is that the two trials of U-WBRT were reported by 2020 coinciding with the worldwide COVID epidemic. The Royal College of Radiologists published in March 2020 guidelines for radiation therapy during the COVID-19 pandemic [32]. These guidelines included using the FAST or FAST-Forward fractionation of 5 fractions only for all patients requiring radiation with node-negative tumors not requiring a boost. In April 2020, an expert opinion from 5 US organizations (American Society of Breast Surgeons, the National Accreditation Program for Breast Centers, the National Comprehensive Care Network, the Commission on Cancer, and the American College of Radiology) recommended M-WBRT be "strongly considered whenever possible" including cases with RNI, and U-WBRT "may be considered" in selected patients not needing RNI [33]. By May 2020, an international guideline with representatives from 12 countries confirmed a recommendation for U-WBRT in most cases needing radiation [16]. In one study from the UK in 2020, the use of U-WBRT for women ≥ 50 increased from < 1% in February

to 70% by April [34]. In another study from Ottawa, the use of U-WBRT increased from close to 0 in 2019 to 40% in 2022 [35].

NCCN currently has a weak recommendation that U-WBRT may be considered using 28.5 Gy in 5 once-a-week fractions like the FAST for selected patients > 50 following BCS with early-stage, node-negative disease particularly in those not requiring a boost [2] M-WBRT remains preferred. And there is only a footnote to suggest the possibility of using 26 Gy in 5 fractions in one week like the FAST-Forward regimen as an alternative. The favoring of FAST by NCCN for U-WBRT is likely due to the caveat of having only 5-year data on local relapse and toxicity so far in the FAST-Forward. This sentiment is consistent with an overall cautionary approach to using U-WBRT in clinical practice in the post-COVID era in the USA. U-WBRT will no doubt have a very slow implantation, particularly for women aged 50–70 (just as it did at first with M-WBRT in the past decade), until more long-term data on breast-related and other toxicity becomes available.

Conclusion

M-WBRT given Monday through Friday over 3–4 weeks is now standard practice for almost all patients needing post-lumpectomy WBRT. The large body of phase III data of M-WBRT versus conventional WBRT shows there is equal long-term local control and the same or lower acute and long-term toxicity as conventional fractionation. M-WBRT can now be safely reduced to 3 weeks in most patients by tumor bed boost that is concurrent rather than sequential based on strong phase III data as well. And M-WBRT may also include even node-positive patients requiring RNI based on existing evidence and international guidelines. Lastly, for more selected patients, including ≥ 50 years and not needing RNI or boost, there is now the option for U-WBRT that shortens treatment to as little as 1 week.

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Data Availability Not applicable.

Declarations

Ethical Approval Not applicable.

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Competing interests The author declares no competing interests.

References

1. Smith BD, Bellon JR, Blitzblau R, Freedman G, Haffty B, Hahn C, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol. 2018;8(3):145–52.
2. National Comprehensive Cancer Network. Invasive Breast Cancer 2023. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 23 May 2023.
3. The Royal College of Radiologists. Postoperative radiotherapy for breast cancer: UK consensus statements 2016. Available from: https://www.rcr.ac.uk/publication/postoperative-radiotherapy-breast-cancer-uk-consensus-statements. Accessed 23 May 2023.
4. 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.
5. Eraso A, Sanz J, Molla M, Reyes V, Pedro A, Arenas M, et al. Evidence-based guidelines for hypofractionated radiation in breast cancer: conclusions of the Catalan expert working group. Clin Transl Oncol. 2022;24(8):1580–7.
6. Ontario CC. Breast irradiation in women with early stage invasive breast cancer following breast conserving surgery 2016. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/841. Accessed 23 May 2023.
7. Wockel A, Festl J, Stuber T, Brust K, Krockenberger M, Heuschmann PU, et al. Interdisciplinary screening, diagnosis, therapy and follow-up of breast cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017): Part 2 with recommendations for the therapy of primary, recurrent and advanced breast cancer. Geburtshilfe Frauenheilkd. 2018;78(11):1056–88.
8. Park YH, Senkus-Konefka E, Im SA, Pentheroudakis G, Saji S, Gupta S, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with early breast cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS. Ann Oncol. 2020;31(4):451–69.
9. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14(11):1086–94.
10. Haviland JS, Mannino M, Griffin C, Porta N, Sydenham M, Bliss JM, et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiother Oncol. 2018;126(1):155–62.
11. Gupta A, Khan AJ, Yegya-Raman N, Sayan M, Ahlawat S, Ohri N, et al. 5-Year results of a prospective phase 2 trial evaluating 3-week hypofractionated whole breast radiation therapy inclusive of a sequential boost. Int J Radiat Oncol Biol Phys. 2019;105(2):267–74.
12. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97(2):116–26.
13. Wang SL, Fang H, Song YW, Wang WH, Hu C, Liu YP, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a

randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol. 2019;20(3):352–60.
14. Leong N, Truong PT, Tankel K, Kwan W, Weir L, Olivotto IA. Hypofractionated nodal radiation therapy for breast cancer was not associated with increased patient-reported arm or brachial plexopathy symptoms. Int J Radiat Oncol Biol Phys. 2017;99(5):1166–72.
15. Bekelman JE, Sylwestrzak G, Barron J, Liu J, Epstein AJ, Freedman G, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008–2013. JAMA. 2014;312(23):2542–50.
16. Coles CE, Aristei C, Bliss J, Boersma L, Brunt AM, Chatterjee S, et al. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. Clin Oncol (R Coll Radiol). 2020;32(5):279–81.
17. Poppe MM, Yehia ZA, Baker C, Goyal S, Toppmeyer D, Kirstein L, et al. 5-Year update of a multi-institution, prospective phase 2 hypofractionated postmastectomy radiation therapy trial. Int J Radiat Oncol Biol Phys. 2020;107(4):694–700.
18 Shaitelman SF, Lei X, Thompson A, Schlembach P, Bloom ES, Arzu IY, et al. Three-year outcomes with hypofractionated versus conventionally fractionated whole-breast irradiation: results of a randomized, noninferiority clinical trial. J Clin Oncol. 2018;36(35):JCO1800317.
19. Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Krause M, et al. Hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma in situ in a randomized phase III trial: the DBCG HYPO trial. J Clin Oncol. 2020;38(31):3615–25.
20. Kindts I, Laenen A, Depuydt T, Weltens C. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane Database Syst Rev. 2017;11(11):CD011987.
21. Jones HA, Antonini N, Hart AA, Peterse JL, Horiot JC, Collin F, et al. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. J Clin Oncol. 2009;27(30):4939–47.
22. Poortmans PM, Collette L, Horiot JC, Van den Bogaert WF, Fourquet A, Kuten A, et al. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. Radiother Oncol. 2009;90(1):80–5.
23. Vicini F, WInter K, Freedman G, Arthur D, Hayman J, Rosenstein B, 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 Radiat Oncol Biol Phys. 2022;114(3):S1.
24. Coles CE, Haviland JS, Kirby AM, Griffin CL, Sydenham MA, Titley JC, et al. Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial. Lancet. 2023. https://doi.org/10.1016/S0140-6736(23)00619-0.
25. Horner-Rieber J, Forster T, Hommertgen A, Haefner MF, Arians N, Konig L, et al. Intensity Modulated Radiation Therapy (IMRT) with simultaneously integrated boost shortens treatment time and is noninferior 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 Radiat Oncol Biol Phys. 2021;109(5):1311–24.
26. Bhattacharya IS, Haviland JS, Perotti C, Eaton D, Gulliford S, Harris E, et al. Is breast seroma after tumour resection associated with patient-reported breast appearance change following radiotherapy? Results from the IMPORT HIGH (CRUK/06/003) trial. Radiother Oncol. 2019;136:190–6.
27. Lee G, Parmar H, Li W, Shessel A. The effect of lumpectomy cavity changes on planning dose in breast radiotherapy boost. J Med Imaging Radiat Sci. 2019;50(2):317–22.
28. Sayan M, Yehia ZA, Jan I, Gupta A, Vergalasova I, Reviello M, et al. Adaptive lumpectomy boost planning can reduce normal tissue exposure in patients receiving hypofractionated whole breast irradiation. Anticancer Res. 2022;42(1):53–7.
29. FAST-Forward Trial Management Group. FAST-Forward Protocol Version 5.1 2018 [Available from: https://www.icr.ac.uk/media/docs/default-source/default-document-library/fast-forward-protocol.pdf?sfvrsn=421a2169_0. Accessed 23 May 2023.
30. Brunt AM, Haviland JS, Sydenham M, Agrawal RK, Algurafi H, Alhasso A, et al. Ten-Year Results of FAST: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol. 2020;38(28):3261–72.
31. Brunt AM, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. 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.
32. The Royal College of Radiologists. Guidelines on radiation therapy for breast cancer during the COVID-19 pandemic 2020. Available from: https://www.rcr.ac.uk/sites/default/files/breast-cancer-treatment-covid19.pdf. Accessed 23 May 2023.
33 Dietz JR, Moran MS, Isakoff SJ, Kurtzman SH, Willey SC, Burstein HJ, et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. Breast Cancer Res Treat. 2020;181(3):487–97.
34. Gannon MR, Dodwell D, Miller K, Horgan K, Clements K, Medina J, et al. Change in the use of fractionation in radiotherapy used for early breast cancer at the start of the COVID-19 Pandemic: a population-based cohort study of older women in England and Wales. Clin Oncol (R Coll Radiol). 2022;34(9):e400–9.
35. Lekx-Toniolo K, Caudrelier J-M. Trends in radiation therapy breast treatments at the Ottawa hospital cancer centre. Presentation at the Canadian Winter School Virtual Meeting 2/1/2023.
36. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol. 2006;7(6):467–71.
37. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362(6):513–20.
38. Wang SL, Fang H, Hu C, Song YW, Wang WH, Jin J, et al. Hypofractionated versus conventional fractionated radiotherapy after breast-conserving surgery in the modern treatment era: a multicenter, randomized controlled trial from China. J Clin Oncol. 2020;38(31):3604–14.