

## Critical Review

# Hypofractionated Postmastectomy Radiation Therapy



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## Abstract

**Purpose:** To provide an overview of the major randomized trials that support the use of hypofractionated post-mastectomy radiation therapy for locally advanced breast cancer patients.

**Methods and Materials:** PubMed was systematically reviewed for publications reporting use of hypofractionated radiation therapy in patients requiring post-mastectomy radiation.

**Results:** Standard fractionation, which is typically delivered over 5 to 7 weeks, is considered the standard of care in setting of post-mastectomy radiation therapy (PMRT). Modern data has helped to establish hypofractionated whole breast irradiation, which consists of a 3- to 4-week regimen, as a new standard of care for early-stage breast cancer. Hypofractionated whole breast irradiation has also laid the groundwork for the exploration of a hypofractionated approach in the setting of hypofractionated post-mastectomy radiation therapy.

**Conclusions:** While standard fractionation remains the most commonly utilized regimen for PMRT, recently published trials support the safety and efficacy of a hypofractionated approach. Ongoing trials are further investigating the use of hypofractionated PMRT.

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## Introduction

Breast cancer is the most common malignancy among women worldwide.<sup>1</sup> Adjuvant radiation therapy (RT) is an important component in the multidisciplinary management in patients with breast cancer. Patients with early stage disease are often treated with breast conserving surgery (BCS) followed by adjuvant RT, with or without systemic agents.<sup>2,3</sup> In the postmastectomy setting, patients with locally advanced disease, such as

node-positive patients, often receive adjuvant RT to the chest wall and draining lymphatics. The benefits of postmastectomy radiation treatment (PMRT) have been demonstrated in multiple randomized trials, as well as the Early Breast Cancer Trialists' Collaborative Group meta-analysis, showing improved survival among patients with locally advanced disease.<sup>4-7</sup>

The most commonly used regimens from prior randomized trials consisted of 1.8 to 2 Gy delivered daily to a total dose of 45 to 50 Gy, with an optional 10 to 16 Gy tumor bed boost. Treatment was delivered to the breast/chest wall with or without regional nodal irradiation. This regimen is referred to as standard fractionation (SF). Hypofractionation consists of delivery of more than 2.0 Gy daily per fraction over 3 to 4 weeks, to a total dose that is

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radiobiologically equivalent to the SF.<sup>8-11</sup> Although the efficacy and tolerability of the SF treatment schedule is well-established, challenges of this prolonged course include inconvenience to the patient, escalation of health care costs, and excess use of resources.<sup>12-17</sup> Using data modeling, Khan et al<sup>18</sup> demonstrated that wide-spread adoption of shorter whole breast irradiation (WBI) or PMRT schedules can result in significantly increased access and improved survival for patients with breast cancer, which is particularly important in regions where RT access is limited. More modern trials designed to compare standard fractionated WBI (SF-WBI) to hypofractionated WBI (HF-WBI) regimens in the setting of BCS demonstrated the safety and efficacy of HF-WBI.<sup>8-11</sup> Updated consensus guidelines have now endorsed an HF approach for the majority of patients receiving WBI after BCS.<sup>19</sup>

The data are now evolving on the use of hypofractionation in the postmastectomy setting. Pending outcomes for ongoing phase III trials, conventional fractionation remains standard of care in this patient population. In this article, we review the available data as well as ongoing randomized trials investigating HF-PMRT.

## Methods and Materials

A detailed literature search for studies published up to October 10, 2020, was implemented with the aid of the PubMed database. Our query identified 373 articles using the search item “postmastectomy radiation therapy” and 22 articles with search item “hypofractionated post-mastectomy.” All titles and abstracts were subsequently screened to identify relevant articles that addressed the use of HF RT in patients requiring postmastectomy radiation. The details of the search results that we incorporated are listed in the references section of our article. Major outcomes in terms of tumor control rates and occurrence of toxicities were extracted from each study to substantiate our article.

## Radiobiological basis and history of hypofractionation

The optimal radiation fractionation schedule must provide maximum tumor cell kill while maintaining

minimum normal tissue toxicity.<sup>20</sup> Keeping this balance is complex and depends on multiple factors including dose per fraction, total dose, and duration of treatment. The linear quadratic radiobiologic model has been developed to describe normal tissue and tumor sensitivity to change in fraction size.<sup>21,22</sup> Historically, most tumor types, including breast cancer, were assumed to be less sensitive to fractionation changes with high  $\alpha/\beta$  ratios of 8 to 10 Gy, whereas most normal tissues were known to be more sensitive to change in fraction size with low  $\alpha/\beta$  ratios of 1 to 4 Gy.<sup>20,23</sup> It was later discovered, however, that breast cancer cell lines have a much lower  $\alpha/\beta$  ratio that is similar to the surrounding normal tissues.<sup>22,24,25</sup> These findings have suggested that a lower total dose in fewer fractions may be more effective than the standard fractionation schemes.<sup>8,26,27</sup>

In addition to this radiobiological evidence, multiple clinical studies in the 1990s reported excellent local control and minimal toxicities with hypofractionation.<sup>28-30</sup> This has led to the initiation of multiple randomized trials to compare the efficacy and safety of hypofractionation with SF in patients with early stage breast cancer. The results of these European and Canadian trials with long-term follow-up have demonstrated that HF-WBI is an appropriate replacement for SF-WBI in most patients.<sup>8,11,31</sup> The radiobiological principles discussed previously, combined with favorable clinical outcomes from large randomized trials with long-term follow-up, have established HF-WBI as the new standard of care.

## Efficacy of HF-PMRT

Multiple retrospective studies support promising outcomes with HF-PMRT (Table 1).<sup>32-36</sup> Although some were largely breast conservation trials, 4 major prospective clinical trials investigating the efficacy and toxicity of various hypofractionation regimens included postmastectomy patients with breast cancer. Key features of these trials are summarized in Table 2.

One of the first major randomized trials was initiated in the United Kingdom in 1999.<sup>9</sup> The UK Standardization of Breast Radiotherapy Trial A (START A) included 2236 patients with T1-3a, N0-1, M0 invasive breast cancer who underwent BCS or mastectomy with surgical margins  $\geq 1$  mm. Patients were randomized to 50 Gy in 25

**Table 1** Retrospective studies on postmastectomy radiation therapy

Author (reference)	Number of patients	Treatment (Gy/fractions)	Follow-up	Local control	Overall survival
Ko et al <sup>32</sup>	133	40/16	5 y	5 y 97.6%	5 y 74.7%
Bochenek-Cibor et al <sup>33</sup>	211	45/20	30 mo	3 y 96.4%	3 y 74.6%
Tovanabutra et al <sup>34</sup>	334	40-48/15-19	66 mo	5 y 96.1%	5 y 64.7%
Eldeeb et al <sup>35</sup>	66	40-45/15-17	23 mo	7 y 95.5%	7 y 92.4%
Kouloulis et al <sup>36</sup>	87	43-48/16-21	36 mo	3 y 100%	NR

Abbreviation: NR = not reported.

**Table 2** Key features of the hypofractionation trials

Variable	START A	START B	Beijing, China	United States
Patients enrolled	2236	2215	820	69
Study years	1998–2002	1999–2001	2008–2016	2010–2014
Median follow-up (y)	9.3	9.9	4.9	4.5
Stage	T1-3a, N0-1, M0	T1-3a, N0-1, M0	T3-4, N2-3, M0	T2-4, N1-3, M0
Surgery				
Lumpectomy, n (%)	1900 (85)	2038 (92)	0	0
Mastectomy, n (%)	336 (15)	117 (8)	820 (100)	69 (100)
Reconstruction, n (%)	—	—	0	41 (59)
Treatment arms (Gy/fractions)	50/25 (5 wk) 41.6/13 (5 wk) 39/13 (5 wk)	50/25 (5 wk) 40/15 (3 wk)	50/25 (5 wk) 43.5/15 (3 wk)	36.6/11 (2.2 wk)
Boost				
n (%)	1159 (61)	875 (43)	0	67 (97)
Dose (Gy/fractions)	10/5	10/5		13.3/4
Regional nodal irradiation, n (%)	318 (14)	161 (7)	820 (100)	69 (100)
Chemotherapy, n (%)	793 (35)	491 (22)	820 (100)	64 (93)

Abbreviation: START = Standardisation of Breast Radiotherapy Trials.

fractions (control arm), 41.6 Gy in 13 fractions (experimental arm), or 39 Gy in 13 fractions (experimental arm). All treatments were delivered over 5 weeks. An elective nonrandomized boost (10 Gy in 5 fractions) was given at the discretion of the treating physician in 61% of patients. A total of 15% of patients underwent mastectomy, 14% received regional nodal irradiation (RNI), and 35% received adjuvant chemotherapy before radiation. At 10 years, rates of local relapse (LR) were 6.7% in the 50 Gy arm, 5.6% in the 41.6 Gy arm, and 8.1% in the 39 Gy arm (*P* value, not significant).<sup>31</sup> Similarly, disease-free survival (DFS) and overall survival (OS) were similar between treatment arms.

The START B trial was initiated in the UK concurrently with the START A trial.<sup>10</sup> Eligibility criteria in this trial were similar to START A. Between 1999 and 2001, 2215 patients were randomized to 50 Gy in 25 fractions (control arm) or 40 Gy in 15 fractions (experimental arms). However, in contrast to the START A trial, the experimental arm completed treatment in only 3 weeks. An elective nonrandomized boost (10 Gy in 5 fractions) was given at the discretion of the treating physician in 43% of patients. A mastectomy was performed in 8% of patients, RNI was delivered in 7% of patients, and chemotherapy was delivered in 22% of patients. At 10 years, rates of LR were 5.2% in the 50 Gy arm and 3.8% in the 40 Gy arm (*P* value, not significant).<sup>31</sup> Surprisingly, distant relapse (16.0% vs 12.3%, *P* = .014) and overall mortality (19.2% vs 15.9%, *P* = .042) were significantly higher in the control arm. Although it is unclear what drove this outcome, it was thought that the difference in LR was likely too small to be a contributing factor.

One of the major hindrances in assessing the benefits of adoption of hypofractionation with RNI is the duration of follow-up. Although results from several limited trials are encouraging, a longer follow-up duration can prove invaluable in arriving at a conclusion regarding the possible utility of hypofractionation with RNI in both locally advanced and postmastectomy settings.

Extrapolating from the START trials can provide some reassurance to treating patients with HF PMRT; however, the questioning of efficacy of this regimen in this more advanced patient population is reasonable. Those patients have more advanced disease and are often treated after surgery and systemic therapy, and one can argue that the residual tumor burden in this group of patients is higher than that in those less advanced patients. Our radiation biology knowledge ensures equivalent tumoricidal activity with hypofractionation; nevertheless, further clinical investigation remains necessary.

It is worth noting the British Columbia Canadian trial, published in *New England Journal of Medicine* in 1997, randomized node positive postmastectomy women to chemotherapy alone versus chemotherapy plus PMRT. The PMRT arm used an HF regimen of 15 fractions in 2.5 Gy per fraction to the chest wall and regional lymph nodes using cobalt machines. At 15 years of follow-up, the HF-PMRT regimen resulted in significant reduction in recurrence rate of 33% (risk ratio, 0.67; 95% confidence interval [CI], 0.50-0.90) and a significant reduction in breast-cancer specific mortality of 29% (risk ratio, 0.71; 95% confidence interval, 0.51-0.99). Although cosmetic outcomes and long-term side effects were not formally evaluated in this study, there were no reports of grade 3 toxicity and they noted no cases of brachial plexopathy at 15 years of follow-up.

More recently, in Beijing, China, 820 patients with locally advanced breast cancer (T3-4 or N2) who underwent mastectomy with axillary lymph node dissection were randomized to SF-PMRT (50 Gy in 25 fractions) or HF-PMRT (43.5 Gy in 16 fractions).<sup>37</sup> All patients received adjuvant (75%) or neoadjuvant (25%) chemotherapy. Radiation treatment was delivered to the unreconstructed chest wall, supraclavicular region, and level III axillary region. The level I to II axillary regions and the internal mammary chain were not targeted. The chest wall was treated with 6 to 9 MeV electrons with a 5-mm tissue equivalent bolus. The supraclavicular region was most commonly treated with a 2-dimensional technique prescribed to a depth of 3 cm beneath the skin. At a median follow-up of 58.5 months, the 5-year cumulative incidence of locoregional recurrence was 8.1% in the SF-PMRT arm and 8.3% in the HF-PMRT arm, indicating that HF-PMRT was noninferior to SF-PMRT. Similarly, DFS (74% vs 70%) and OS (84% vs 86%) did not significantly differ between the arms. Given the eligibility criteria that included patients with advanced disease as detailed previously, those equivalent findings at 5 years are reassuring. However, we acknowledge the limitations to applying these data to the patients in the United States (US) given the differences in the technology used, such as the use of electron fields, 2-dimensional RT, and omission of internal mammary nodes coverage. Also, in this study, only 55% of patients with HER2-positive cancers were treated with trastuzumab. This may have meaningful implications when extrapolating long-term toxicity, particularly cardiac toxicity outcomes.

In the United States, a prospective phase II HF-PMRT trial enrolled 96 patients to receive a dose of 36.63 Gy in 11 fractions, delivered 5 days a week, to the chest wall or reconstructed breast and the regional lymphatics.<sup>38</sup> Eligible patients had stage IIA to IIIC invasive breast cancer and were allowed to undergo breast reconstruction, receive neoadjuvant/adjuvant chemotherapy, and antihormone therapy. High-risk features such as lympho-vascular invasion, close margins, young age, and negative hormone receptors were allowed in this study. Coverage of the internal mammary nodes was not required but occurred in 54% of patients. An optional mastectomy scar boost (3.33 Gy  $\times$  4 fractions) was given at the discretion of the treating physician in 97% of patients. Forty-three patients (45%) underwent breast reconstruction (93% underwent reconstruction before HF-PMRT and 7% after HF-PMRT). The primary endpoint was freedom from grade 3 or higher late nonreconstruction-related radiation toxicities. At a median follow-up of 54 months, there were no acute or late grade 3 and 4 nonreconstruction toxicities. At 5 years, the rate of locoregional recurrence was 4.6%, distant DFS 77%, and OS 90%.<sup>39</sup>

## Acute toxicity

The START A and B trials did not report on acute toxicity; however, in the HF-PMRT trial from China, overall acute grade 3 skin toxicity was significantly reduced with HF-PMRT compared with SF-PMRT (3% vs 8%,  $P < .0001$ ).<sup>37</sup> Otherwise, there were no significant differences between groups in the incidence of other acute toxicities. In the US phase II HF-PMRT trial, there were no acute grade 3 toxicities, and only 24% of the patients reported acute grade 2 skin toxicity.<sup>38</sup> Additionally, a number of retrospective studies have reported that patients who received HF-PMRT experienced significantly lower or similar rates of acute skin toxicity compared with those who received SF-PMRT.<sup>32-34,36,40,41</sup>

## Late toxicity

In START trials, rates of late toxicities (including breast shrinkage, arm edema, shoulder stiffness, telangiectasias) either favored HF-PMRT or were similar between HF-PMRT and SF-PMRT. Long-term analysis of these trials also showed very low rates of ischemic heart disease (0.8% in START A and 1.1% in START B), symptomatic rib fractures (0.1% in START A and 0.3% in START B), and radiation pneumonitis (0.1% in START A and 0.5% in START B), with no differences between HF-PMRT and SF-PMRT.<sup>31,42</sup> In the HF-PMRT trial from China, there were no significant differences in late toxicities between the HF-PMRT and SF-PMRT arms, including radiation pneumonitis (grade  $\leq$  2, 15% vs 10%;  $P = .081$ ), lymphedema (grade  $\leq$  3, 20% vs 21%;  $P = .961$ ), ischemic heart disease (grade  $\leq$  3, 1.7% vs 1%;  $P = .569$ ), and shoulder dysfunction (grade  $\leq$  3, 2% vs 3.4%;  $P = .734$ ).<sup>37</sup> In the US HF-PMRT trial, no grade 3 late toxicities were reported. The most common late toxicity was grade 1 skin toxicity, occurring in 30% of the patients, usually as hyperpigmentation. Long-term analysis of this trial additionally showed a low rate of grade 2 toxicities, including chest wall pain (8%), fatigue (3%), and lymphedema (2%).<sup>39</sup>

Although radiation-induced brachial plexopathy is a concern, this has become an increasingly rare entity in patients receiving HF-PMRT in the modern era (Table 3).<sup>8,31,37,39,43-53</sup> According to Galecki et al,<sup>51</sup> the risk of radiation-induced plexopathy was less than 1% when the total dose administered was in the range of 34 to 40 Gy. Surgical manipulation and chemotherapy are additional factors that can lead to brachial plexopathy.<sup>51</sup> It has also been reported that when the biological effective dose exceeds 55 Gy, the risk of radiation-induced brachial plexopathy increases rapidly.<sup>51</sup> The 2 Gy equivalent dose (EQD2) of historic HF-PMRT regimens are estimated to be significantly higher than the tolerance of brachial plexus.<sup>38</sup> A Swedish study with estimated EQD2 of 76 Gy

**Table 3** The brachial plexopathy rate with postmastectomy radiation therapy or regional nodal irradiation

First author	Period	Patient no.	RNI dose (Gy)	Fractions	EQD <sub>2</sub> *	Plexopathy rate (%)	Median follow-up (yr)
Stoll <sup>43</sup>	1958-1962	117, PMRT	63	12	114.2	73	2.5
Johansson <sup>44</sup>	1963-1965	71, PMRT	57	17	76.3	63	34
Bajrovic <sup>45</sup>	1980-1993	140, RNI	52	20	59.8	14	8
Bates <sup>46</sup>	1968-1974	411, PMRT	35	6	68.5	NR	10
			50	12	77.1	NR	
Baillet <sup>47</sup>	1984-1989	230, RNI not reported	23	4	44.6	NR	5
Rodger <sup>48</sup>	1979-1982	484, PMRT and RNI	45	10	66.4	1	10
	1982-1984	289, PMRT and RNI	45	20	43.8	1	
Ragaz <sup>49</sup>	1979-1986	318 (164 PMRT)	35	16	37	0	20
Powell <sup>50</sup>	1982-1984	338	45	15	56	6	5.5
		111	54	30	51	1	
Owen <sup>8</sup>	1986-1998	290 (2/3rd HF)	42.9	13	47-49	0	8
			39				
Haviland <sup>31</sup>	1998-2002	479 (278 HF)	40	13-15	47-49	<1	9.3
			42.9				
			39				
Wang <sup>37</sup>	2008-2016	820, PMRT and RNI	50	25	50	0	4.9
			43.5	15	53.3		
Poppe <sup>39</sup>	2010-2014	69, PMRT and RNI	36.6	11	48.7	0	4.5

Abbreviations: EQD<sub>2</sub> = 2-Gy equivalent dose; HF = hypofractionated; NR = not reported; PMRT = postmastectomy radiation therapy; RNI = regional nodal irradiation.

\* Alpha/beta ratio of 2 Gy assumed for normal tissues in EQD<sub>2</sub> calculations.

and an Australian study with estimated EQD<sub>2</sub> of 114 Gy reported very high rates of brachial plexopathy, at 63% and 73%, respectively.<sup>43,44</sup> With better understanding of the radiobiology of breast cancer and development of modern planning and treatment techniques, the rate of radiation-induced brachial plexopathy has decreased over time.<sup>49,50</sup> There was only 1 reported case of brachial plexopathy among all patients treated in the START trials. There were no cases of brachial plexopathy in the recently published trials from China or the United States.

A study by Haviland et al<sup>54</sup> analyzed the results of adjuvant lymph node RT in START-A and START-B trials, focusing on the late normal tissue effects of the arm and shoulder. They observed that there was no statistically significant difference in physician-assessed shoulder stiffness and arm edema between the HF schedules and control groups in both START-A and START-B groups. They thus concluded that HF RT is relatively safe when appropriately dosed.

The Selective Use of Postoperative Radiotherapy after Mastectomy trial, a randomized, controlled trial included 1688 patients with intermediate-risk breast cancer and was aimed at understanding the quality of life (QOL) after postmastectomy RT.<sup>55</sup> Velikova et al<sup>55</sup> found that no differences were noted between the treatment and control groups in fatigue, shoulder and arm symptoms, body image, physical function, and overall QOL. However, they noted that patients who received postmastectomy RT had significantly higher localized chest wall symptoms for up to 2 years postradiation compared with the no-RT group.

## Breast reconstruction and cosmesis

Although 15% of the patients in START A and 8% in START B trials underwent mastectomy, there was no description of breast reconstruction in these patients. Assessment of the moderate or marked breast change in all patients of the START trials favored HF-WBI over SF-WBI at 10 years.<sup>31</sup> Breast shrinkage and induration were the most common late normal tissue effects in the START trials. Moderate or marked breast shrinkage, telangiectasia, and breast edema were significantly lower with HF-WBI than with SF-WBI.<sup>31</sup> Furthermore, patients randomized to HF-WBI in the START B trial were less likely to have a change in skin appearance based on photographic and patient self-assessments.<sup>10</sup>

Breast reconstruction after mastectomy has become more common and has been shown to provide a significant improvement in most QOL measures.<sup>56-63</sup> Studies have demonstrated that SF-PMRT after breast reconstruction increases reconstructive complication rates.<sup>64-69</sup> A meta-analysis of 6257 patients treated by SF-PMRT reported a reconstructive complication rate of 41% in implant-based reconstruction, including a reconstruction failure rate of 17%, an infection rate of 13.5%, and a capsular contracture rate of 38%.<sup>70</sup> The HF-PMRT trial from China was limited to patients who did not undergo breast reconstruction.<sup>37</sup> However, in the US phase II HF-PMRT trial, 43 patients (45%) underwent breast reconstruction.<sup>39</sup> Reconstructions were commonly performed before HF-PMRT (93%) and consisted of temporary expanders (88%), permanent implants (7%),

and prior augmentation implants (5%). A total of 35% of the patients had grade 3 or 4 reconstruction complications attributable to RT in this trial.

## Future directions

Based on the available data, HF-PMRT appears noninferior to and has similar toxicities to SF-PMRT in patients with high-risk breast cancer on short-term follow-up. A meta-analysis and systematic review by Liu et al<sup>71</sup> included 25 clinical trials with a total of 3871 postmastectomy patients with breast cancer. They concluded that HF RT was not significantly different in either efficacy or toxicity compared with conventional RT in this patient population and emphasized the need for larger randomized control trials. However, data on the safety of HF-PMRT in patients with breast reconstruction remain limited. Ideally, it is anticipated that HF-PMRT would minimize the frequency of complications without compromising cosmesis. As the use of breast reconstruction increases, it becomes particularly important to understand the relationship between RT regimen and reconstructive outcomes. The ongoing Alliance A221505 trial (RT CHARM: phase III Randomized Trial of Hypofractionated Post Mastectomy Radiation with Breast Reconstruction) is randomizing patients undergoing mastectomy with immediate or delayed reconstruction to HF-PMRT (42.56 Gy in 16 fractions) or SF-PMRT (50 Gy in 25 fractions). RNI with the same dose regimen is required, but mastectomy scar boost is not allowed. The target enrollment is 880 patients with a primary endpoint of reconstruction complication rate. Secondary endpoints include recurrence free survival and toxicities, including brachial plexopathy and lymphedema. Another ongoing trial (FABREC: Study of Radiation Fractionation on Patient Outcomes After Breast REConstruction for Invasive Breast Carcinoma) is randomizing patients undergoing mastectomy with immediate reconstruction to HF-PMRT (42.56 Gy in 16 fractions) or SF-PMRT (50 Gy in 25 fractions). The primary endpoint of this trial is the patient-reported outcomes at 6 months.

## Conclusions

For decades, adjuvant RT has been an established standard of care after mastectomy for locally advanced breast cancer. Although standard fractionation over a course of 5 to 7 weeks has been historically used to achieve excellent tumor control with low toxicity, this regimen can be inconvenient for patients and can increase health care costs. Although HF-WBI has been established as a standard of care for the majority of patients with early-stage breast cancer, the expanded use of an HF approach in the settings of postmastectomy and regional

nodal irradiation is an area of active investigation. Early results support the safety and efficacy of HF-PMRT. Based on long-term data and results of ongoing trials, HF-PMRT may evolve into a new standard of care.

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