Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(2): 41
https://doi.org/10.31083/j.ceog5002041

Review

Hypofractionated Postmastectomy Radiotherapy (HF-PMRT): What did We Learn from COVID-19 Era?

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Academic Editor: Christos Iavazzo
Submitted: 28 July 2022 Revised: 12 November 2022 Accepted: 29 November 2022 Published: 8 February 2023

Abstract

Objectives: In breast cancer (BC) patients receiving mastectomy, postmastectomy radiotherapy (PMRT) improves long-term outcomes by decreasing local failure and cancer mortality. However, the optimal PMRT schedule is still under investigation. The present review aims to discuss the evidence regarding hypofractionated (HF) PMRT in BC patients in order to identify the optimal treatment approach. Additional purpose is to highlight what we have learned from COVID-19 era regarding HF schedules for PMRT in BC patients. **Mechanism**: Between February and November 2021, literature and database research were conducted. Key references were detected from a PubMed query. Range of publication date was between 2000 and 2021. Selection criteria included English language publications in humans. Hand searching included meeting proceedings of the European Society for Radiotherapy and Oncology (ESTRO), European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO). The website clinicaltrials.gov was also searched. Randomized controlled trials evaluating HF-PMRT were included. **Findings in brief**: Our research returned 87 published papers. Fourteen trials were included in our final analysis. The comparisons of several different schedules of HF-PMRT with conventional fractionated PMRT provided similar results in terms of locoregional disease control without increasing toxicity. Particularly, an acute skin toxicity incidence grade 2 or higher ranged between 10 and 25% among the studies we analyzed. **Conclusions**: The present paper suggests that safety and efficacy of HF-PMRT is comparable with conventional schedules and standard practice guidelines are already available. COVID-19 pandemic has emphasised the need for increasingly tailored treatment protocols. Modern HF regimens should continue to be the standard of treatment in BC patients who receive PMRT also in the post-COVID-19 era.

Keywords: breast cancer; hypofractionated post-mastectomy radiotherapy; conventional fractionated PMRT; COVID-19 pandemics

1. Introduction

The standard of care for patients affected by early invasive breast cancer (BC) is currently whole-breast irradiation (WBI) after breast-conserving surgery (BCS). WBI reported a reduction in first relapse with a lower absolute 10-year risk decrease of any locoregional or distant recurrence [1]. Currently, shorter schedules based on moderate hypofractionated regimens should be the standard of care for WBI reporting a level-1 evidence on equivalent locoregional control and late toxicity rates [2]. Recently, a brand-new approach in adjuvant breast radiation therapy is the ultra-hypofractionated schedule given over just one-week, feasible in selected low-risk patients. In this regard, the FAST Forward trial compared 26 Gray (Gy) or 27 Gy in 5 fractions over 1 week to 40 Gy in 15 fractions over 3 weeks. At 5 years, the two experimental regimens proved to be non-inferior to control group regarding local recurrence, with a safety profile in favor of 26 Gy in 5 fractions as compared to a total dose of 27 Gy [3]. If we advocate BC patients who received mastectomy, it is well known that post-mastectomy radiotherapy (PMRT) improves long-term outcomes by decreasing local failure and cancer mortality [4–6]. The use of PMRT has been widely validated for patients with four or more positive lymph nodes but there are still questions regarding the value of PMRT for those with one to three positive nodes [6]. Moreover, patients with axillary nodal involvement persistent after primary systemic therapy should receive PMRT [6]. According to the National Comprehensive Cancer Network (NCCN) panel, the recommended schedule for PMRT is a conventional regimen of

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46–50 Gy delivered in 23–25 fractions to the chest wall [7]. However, the optimal PMRT schedule is still controversial and underreported. In the last decades, many authors have investigated the reduction of toxicity, overall treatment time and cost thanks to the adoption of hypofractionated regimen after mastectomy [8]. High-quality data coming from five-fraction randomized clinical trials have catalyzed the interest of the radiation oncology community in the implementation of hypofractionated schedules. In this context, the still ongoing COVID-19 pandemic has reinforced the urgent need also to minimize exposure of patients to virus without compromising oncological outcome [9,10]. The aim of the present critical overview is to discuss the evidence regarding hypofractionated (HF) PMRT in BC patients in order to identify the current treatment approach. Therefore, the additional purpose of the present paper is to highlight what we have learned from COVID-19 era regarding HF schedules for PMRT in BC patients.

2. Methods

Between February and November 2021, we conducted literature and database research. Key references were retrieved from a PubMed query, using the combination of the following keywords: (*chest wall* OR *thoracic wall*) AND (*breast cancer* OR *breast neoplasm* OR *breast* OR *mastectomy*) AND (*hypofractionated*) AND (*radiotherapy* OR *radiation treatment* OR *radiation therapy* OR *postmastectomy radiotherapy*). The range of publication date was between 2000 and 2021. Selection criteria included English language publications in humans. Hand searching included meeting proceedings of the European Society for Radiotherapy and Oncology (ESTRO), European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO). The website clinicaltrials.gov was also searched. Reference lists of the identified studies were explored and cross references were allowed. We removed duplicates and excluded studies which did not report a correct population, study design, type of treatment, survival outcome and completeness of published data. Data extraction was conducted independently by two researchers (VSa and IMo) and disagreements were resolved on a case-by-case basis with a discussion among three co-authors (ID, CB, LV).

3. Results

Randomized controlled trials evaluating HF-PMRT were included in the analysis. Our research returned 87 published papers. Fourteen trials were included in our final analysis and main findings are summarized in Table 1 (Ref. [2,3,11–22]). All patients included between 1998 and 2017 had early or locally advanced invasive breast cancer without distant metastases and underwent breast conservative surgery or, in most cases, mastectomy. All received adjuvant radiation treatment, whereas systemic therapy either with neoadjuvant or adjuvant intent was delivered according to physician's choice in consideration of additional risk factors. Patients were assigned to conventional fractionation treatment (50 Gy in 25 fractions) or to a hypofractionated schedule which varied among studies. Primary endpoint used to measure the efficacy of hypofractionated radiation treatment in comparison with a conventional schedule was locoregional control, in terms of recurrence in the ipsilateral breast/chest wall or regional nodal basin. Toxicity rates were also reported, with a specific focus on cutaneous adverse events. In most studies HF-PMRT proved non-inferior to conventional fractionated (CF)-PMRT in terms of locoregional control and skin reactions. All hypofractionated schedules reported the same response and favorable outcomes. Just one study [15] resulted in higher acute skin reactions in the HF group, but no significant difference was detected for what concerns local recurrence or late radiation-induced effects. Hypofractionation also showed the advantage of reducing overall treatment time, treatment burden and cost, with a consequent better compliance to therapy.

4. Discussion

In clinical trials investigating hypofractionated regimens, most of patients enrolled received WBI and data about chest wall and regional nodal irradiation are currently missing. Therefore, the role of HF-PMRT is debated and still underreported. Recently Marta *et al*. [10] conducted a critical review on the adoption of moderately hypofractionated post-operative radiation therapy for BC suggesting that there is no radiobiological evidence that patients treated with HF-PMRT should report different outcomes. However, the lack of consensus among the authors has resulted in the unmet need for the optimal management of BC patients receiving PMRT. With this regard, data coming from a randomized, non-inferiority, open-label, phase 3 trial reported that HF-PMRT was non-inferior to and had similar toxicities to conventional fractionated radiation therapy in patients with high-risk BC [11]. Wang *et al*. [11] evaluated 810 patients with locally advanced BC showing no significant differences in the 5-year incidence of locoregional failure, overall survival or disease-free survival between HF-PMRT with conventional fractionated (CF) PMRT. Furthermore, acute and late period side effects of treatments were comparable in two groups [11]. Additionally, the FAST-Forward trial provided strong evidence referring to the adoption of ultra-hypofractionated schedules (26 Gy in 5 daily fractions) in early BC [3]. Notwithstanding the restricted sample of patients receiving HF-PMRT, the authors concluded that the five-fraction regimen may be adopted as a new standard approach for patients with BC who received whole breast or chest wall irradiation. Furthermore, 15% and 8% of patients treated with HF-PMRT were enrolled in the START-A and START-B studies, respectively. The UK trial reported no significant difference in terms of local

Table 1. Clinical trials of hypofractionated postmastectomy radiotherapy.

Study	Year	N. of pts	Eligible patients	RT schedule	N. of pts undergoing mastectomy (%)	Locoregional control	Toxicity rates (breast or chest wall)	Main findings for HF-PMRT
Brunt M *et al.* [3]	2011–2014	4096	Invasive BC (pT1–3, pN0–1, M0)	40 Gy in 15 fr	40 Gy-S: 6.7%	IBTR 40 Gy-S: 2.3%	40 Gy-S: 10.6%	26 Gy in 5 daily fractions as a new standard for operable BC requiring adjuvant RT to partial or whole breast
				27 Gy in 5 fr	27 Gy-S: 6.5%	27 Gy-S: 2.0%	27 Gy-S: 15.9%	
				26 Gy in 5 fr	26 Gy-S: 6.1%	26 Gy-S: 1.5%	26 Gy-S: 12.2%	
Wang SL *et al.* [11]	2008–2016	810	Invasive BC (pT3-pT4 or ≥pN1)	50 Gy in 25 fr	50 Gy-S: 100%	LRR 50 Gy-S: 7.1%	50 Gy-S: 3% (G3)	HF-PMRT non-inferior to and with similar toxicity profile to conventional fractionated RT in patients with HR-BC
				43.5 Gy in 15 fr	43.5 Gy-S: 100%	43.5 Gy-S: 7.7%	43.5 Gy-S: 8% (G3)	
Haviland JS *et al.* [2]	1999–2002	A: 2236 B: 2215	Invasive BC (pT1-3a, pN0–1, M0)	START-A: 50 Gy in 25 fr 41.6 Gy or 39 Gy in 13 fr	START-A 50 Gy-S: 15.8% 41.6 Gy-S: 14.5% 39 Gy-S: 14.5%	LRR START-A 39 Gy-S: 8.8% 41.6 Gy-S: 6.3% 50 Gy-S: 7.4%	START-A: less common in the 39 Gy-S vs 50 Gy-S; no difference between 41.6 Gy-S and 50 Gy-S	Hypofractionated radiotherapy safe and effective for patients with early BC
				START-B: 50 Gy in 25 fr 40 Gy in 15 fr	START-B 50 Gy-S: 7.7% 40 Gy-S: 8.3%	START-B 40 Gy-S: 4.3% 50 Gy-S: 5.5%	START-B: less common in the 40 Gy-S vs 50 Gy-S	
Shahid A *et al.* [12]	1998–2004	300	Invasive BC (pT2–4, N any)	27 Gy in 5 fr	27 Gy-S: NR	LRR 27 Gy-S: 11%	27 Gy-S: 37% (G3-4)	All hypofractionated protocols equally effective in LR control and toxicity
				35Gy in 10 fr 40Gy in 15 fr	35Gy-S: NR 40Gy-S: NR	35Gy-S: 12% 40Gy-S: 10%	35Gy-S: 28% (G3-4) 40Gy-S: 14% (G3-4)	
Abihilash GH *et al.* [13]	NR	60	Invasive BC (stage II–III), mastectomy	39 Gy in 13 fr	39 Gy-S: 100%	IBTR 39 Gy-S: 13.3%	39 Gy-S: 3.3% (G3 acute), 3.3% (G4 acute), 13.3% (G2 late)	Hypofractionated schedules show same tumor control and late normal tissue effects
				50 Gy in 25 fr	50 Gy-S: 100%	50 Gy-S: 10%	50 Gy-S: 3.3% (G3 acute), 19% (G2 late)	
Das P *et al.* [14]	2013–2015	108	Early and locally advanced stage, mastectomy	50 Gy in 25 fr	50 Gy-S: 100%	IBTR 50 Gy-S: 9.4%	50 Gy-S: 75.4% (G1 acute), 73.6% (G1 late)	HFRT and CFRT similar results in terms of LR control and toxicity profile
				42.56 Gy in 16 fr	42.56 Gy-S: 100%	42.56 Gy-S: 11%	42.56 Gy-S: 76.3% (G1 acute), 72.7% (G1 late)	
Eldeeb H *et al.* [15]	2001–2004	107	Early and locally advanced stage, modified radical mastectomy	50 Gy in 25 fr	50 Gy-S: 100%	IBTR 50 Gy-S: 7.3%	50 Gy-S: 5% (G2 acute)	Acute skin reactions higher in the hypofractionated arms, but no significant difference in the local recurrence or late radiation effects
				45 Gy in 17 fr	45 Gy-S: 100%	45 Gy-S: 2.8%	45 Gy-S: 28% (G2 acute), 5.6% (G3 acute)	
				40 Gy in 15 fr	40 Gy-S: 100%	40 Gy-S: 6.7%	40 Gy-S: 30% (G2 acute), 6.7% (G3 acute)	

Table 1. Continued.

Study	Year	N. of pts	Eligible patients	RT schedule	N. of pts undergoing mastectomy (%)	Locoregional control	Toxicity rates (breast or chest wall)	Main findings for HF-PMRT
Fatma MFA *et al.* [16]	2015–2017	100	BC and surgical intervention by modified radical mastectomy (MRM) and axillary dissection	40 Gy in 15 fr 50 Gy in 25 fr	40 Gy-S: 100% 50 Gy-S: 100%	IBTR 40 Gy-S: 4.2% 50 Gy-S: 6.7%	40 Gy-S: 16% (G2 acute), 8% (late) 50 Gy-S: 20% (G2 acute), 6% (G1 late), 4% (G2 late)	PM-HFRT comparable survival and toxicity with shorter overall treatment time, treatment burden and cost
Kalita AK *et al.* [17]	2014–2015	50	Age >18 years, stage II–III, or neoadjuvant chemotherapy with normal haematological, cardiac and pulmonary functions. Modified radical mastectomy	50 Gy in 25 fr 40 Gy in 15 fr	50 Gy-S: 100% 40 Gy-S: 100%	NR	50 Gy-S: 28% (G2 acute), 8% (G3 acute) 40 Gy-S: 16% (G2 acute)	HF-PMRT showed lesser acute toxicities, was better in terms of treatment compliance and hence can be used routinely
Kouloulias V *et al.* [18]	2008–2011	117	33–78 years, T2-4 primary lesion and N1, N2, N3, or Nx nodal status. Post-mastectomy status evaluation with axillary dissection	48.3 Gy in 21 fr 42.56 Gy in 16 fr 50 Gy in 25 fr	48.3 Gy-S: 100% 42.56 Gy-S: 100% 50 Gy-S: 100%	0% in all groups	48.3 Gy-S: 35% (G2 acute), 6.7% (G3 acute), 16.7 % (G1 late) 42.56 Gy-S: 25.9% (G2 acute), 3.7% (G3 late), 25.9% (G1 kate) 50 Gy-S: 40% (G2 acute), 26.7% (late G1)	All schedules equally effective with equivalent toxicity
Kumbhaj P *et al.* [19]	NR	91	Modified radical mastectomy, radiotherapy and chemotherapy naive, KPS >70	50 Gy in 25 fr 40 Gy in 17 fr	50 Gy-S: 100% 40 Gy-S: 100%	50 Gy-S: chest failure 5%; axillar lymph node failure 8% 40 Gy-S: chest failure 9%; axillar lymph node failure 7%	50 Gy-S: 45% (G2); 5% (G3) 40 Gy-S: 50% (G2), 20% (G3)	HF-PMRT and CF-PMRT equally efficacious in terms of locoregional control, acute and late toxicities
Purohit R *et al.* [20]	Jan 2014–Dec 2014	50	Post-MRM carcinoma; breast stage IIA-IIIA, PS 0–2	50 Gy in 25 fr 40 Gy in 15 fr	50 Gy-S: 100% 40 Gy-S: 100%	NR	50 Gy-S: 28% (G2), 12% (G3) 40 Gy-S: 8% (G2), 4% (G3)	Hypo-fractionation schedule feasible as a standard form of treatment in post-mastectomy patients
Rastogi K *et al.* [21]	NR	100	Postmastectomy patients, >18 years, PS 0–2	50 Gy in 25 fr 42.72 Gy in 16 fr	50 Gy-S: 100% 42.72 Gy-S: 100%	50 Gy: chest wall recurrence 2%, nodal recurrence 0% 42.72 Gy: chest wall recurrence 0%, nodal recurrence 2%	50 Gy-S: 40% (>G2 acute), 4% (>G2 late) 42.72 Gy-S: 42% (>G2 acute); 4% (>G2 late)	HF-PMRT is comparable to conventional RT without evidence of higher adverse effects or inferior locoregional tumor control in adjuvant setting
El Sayed M *et al.* [22]	2001–2012	343	Histologically confirmed infiltrating duct carcinoma, no distant metastases. Surgical resection (MRM or BCS), adjuvant systemic and radiation therapy	50 Gy in 25 fr 42.5 Gy in 16 fr 39 Gy in 13 fr	50 Gy-S: 51.9% 42.5 Gy-S or 39 Gy-S: 87.8%	DFS 50 Gy-S: 86.5% HF-S: 83.8 %	50 Gy-S: 25% (G2 acute); 5% (late) 42.5 Gy-S/39 Gy-S: 9% (G2 acute), 10% (late)	HFRT resulted in OS rate comparable to that of CFRT without inferior local tumour control or higher adverse effects

CI, confidence interval; NR, not reported; IBTR, ipsilateral breast tumour relapse; LRR, locoregional relapses; BC, breast cancer; -S, schedule; HR, high-risk; HF-PMRT, hypofractionated post-mastectomy radiotherapy; G, grade; pts, patients; DFS, disease free survival; fr, fraction; RT, radiotherapy; Gy, Gray; N. number; HF, hypofractionated; PMRT, post-mastectomy radiotherapy; LR, local relapse; HFRT, hypofractionated RT; CFRT, conventional fractionated RT; PM, post-mastectomy; OS, overall survival.

recurrence or late RT-related side effects between the two arms after 10 years of follow-up [2]. To the best of our knowledge, the comparisons of a number of different schedules of HF-PMRT with CF-PMRT provided comparable results in terms of locoregional disease control without the increase of toxicity [2,3,11–22]. Particularly, an acute skin toxicity incidence grade 2 or higher ranged between 10 and 25% among the studies we analyzed [2,3,11–22]. In line with the literature, the meta-analysis and systematic review of Liu *et al*. [8] reported a rate of skin reactions in the acute period of 17.3%. Similarly, the subgroup of patients who received HF-PMRT of the UK START study was 12% and no significant difference was collected in terms of lymphedema or moderate/marked breast symptoms [2]. The above-mentioned findings suggest that HF-PMRT may provide a good tolerability profile confirming high rates of local control of disease for high-risk breast cancer patients. Clinically, the adoption of HF-PMRT could decrease workload, cost of oncological care, increase compliance and allow the treatment of more patients. Despite the number of patients receiving HF-PMRT is increasing worldwide, there is still the need for general consensus regarding the optimal schedules of PMRT. Therefore, Meattini *et al*. [23] recently published the findings from the European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice confirming that hypofractionated radiotherapy can be adopted for the treatment of whole breast, chest wall, and nodal volumes. Moreover, the consensus states that ultra- hypofractionated schedules can also be offered for breast or chest wall in patients who received mastectomy without reconstruction and no nodal involvement [23]. In the last two years, the rapid escalation of severe acute respiratory syndrome coronavirus (SARS-CoV)-2-related disease (COVID-19) led to the need of guidelines for prioritizing health services and procedures [24]. Cancer patients have been identified as a fragile population due to their comorbidity. In this regard, many authors have focused their efforts on minimizing the possibility of infection without compromising the oncological outcome of cancer patients [25,26]. Concerning the low/intermediate-risk patients with breast cancer, ESMO guidelines recommended that the use of hypofractionated regimens for adjuvant postoperative radiotherapy should be considered to reduce hospital visits [25]. Similarly, Coles *et al*. [26] stated that the moderate hypofractionation should be adopted for the whole breast, chest wall and nodal radiotherapy during the COVID-19 Pandemic. In conclusion, the results of our literature review highlighted that safety and efficacy of HF-PMRT is comparable with conventional schedules, but prospective studies and further randomized controlled trials (RCTs) are expected. However, COVID-19 pandemic has enhanced the need for increasingly personalized treatment protocols. With similar toxicity profile and oncological outcome, the optimal radiotherapy schedule should be based on the tumor biology, risk of disease and patients' characteristics, taking into consideration also the reduction of overall treatment time and cost. Modern hypofractionated regimens should continue to be the standard of care in breast cancer patients who receive PMRT also in the post-COVID-19 era.

Author Contributions

VSa, CB, LV, ID, IMe and LL gave the idea and wrote the main manuscript text. VSc, MB, LO, SB, GF and JN wrote the method of the critical review. ES, CC, IB, NB, BB and IMo reviewed references and prepared the table. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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