Hypofractionated whole breast radiation: how low can you go?

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Abstract: Breast conserving therapy (BCT), consisting of breast conserving surgery (BCS) followed by whole breast radiation therapy (WBRT), is a well-established standard for the treatment of women with ductal carcinoma in situ (DCIS) and early-stage invasive breast cancer. While the original trials establishing this paradigm utilized conventionally fractionated (CF-WBRT) treatment delivered with daily fractions over 5–7 weeks, there is a significant amount of level I evidence in support of standardly using hypofractionated (HF-WBRT) regimens delivered over 3–4 weeks, and now there is data supporting even shorter courses. This article reviews the historical basis for CF-WBRT and subsequent radiobiological reasoning for attempting HF-WBRT. Summarized herein are the major clinical trials that have established the safety and efficacy of HF-WBRT as the standard of care in almost all women receiving BCT for early stage, node-negative breast cancer which form the basis of the American Society for Radiation Oncology (ASTRO) consensus statements. Completed and ongoing clinical trials that are attempting to establish the role of hypofractionated (HF) regimens for patients who require regional nodal irradiation as part of post-mastectomy radiation therapy (PMRT) are presented. Recently, published data on ultra-hypofractionated courses are reviewed. Finally, there is a discussion of adoption of hypofractionation globally. The goal of this review is to provide a rationale for the routine use of HF courses to improve patient access and convenience, healthcare resource utilization, and potentially decreasing patient exposure in the setting of the ongoing global pandemic.

Keywords: Hypofractionation; whole breast radiation; ultra-hypofractionation

Introduction

A standard treatment for early-stage breast cancer is breast conserving therapy (BCT), defined as breast conserving surgery (BCS) followed by adjuvant radiation therapy (RT) and the potential addition of systemic therapy. Several randomized clinical trials (RCTs) have established that BCT leads to excellent locoregional control, breast preservation, and survival comparable to mastectomy (1-3). The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has published meta-analyses in both early-stage invasive breast cancer (4) and ductal carcinoma in situ (DCIS) (5) assessing the benefit of adjuvant RT after BCS. In the case of invasive disease, the addition of RT after BCS leads to an absolute benefit of 15.7% in terms of recurrence risk, which translates to a 3.8% breast cancer mortality benefit at 15 years. In the case of DCIS, patient level data from 3,729 women enrolled in four randomized trials was reviewed and revealed that adjuvant RT approximately halves the risk of an ipsilateral breast event after BCS at 10 years (28.1% *vs.* 12.9%). A benefit was maintained regardless of age, margin status, grade, size, and tamoxifen use. Unsurprisingly, no

effect was seen on breast cancer mortality or death from any cause.

Almost all of the data that initially supported the use of adjuvant RT as part of BCT was based on conventionally fractionated courses of whole breast radiation therapy (CF-WBRT), which is delivered in small daily doses or fractions [1.8–2 Gray (Gy)] over 5–7 weeks. This was based off of significant toxicity seen with initial hypofractionated courses (HF-WBRT) (6,7), and inaccurate assumptions about the inherent radiosensitivity of breast cancer. Radiobiologic studies in cell lines would eventually demonstrate that breast cancer cell lines are more sensitive to fraction size than was originally anticipated (8-10). This data, along with an interest in shortening radiation courses for patient convenience and improved resource utilization, led to the development of multiple phase III RCTs to compare 3–4-week courses of HF-WBRT to CF-WBRT.

In this article, we discuss the radiobiologic basis of HF-WBRT in early-stage breast cancer and review the randomized data in support of 3–4-week daily RT, along with shorter (ultra-hypofractionated) courses. We will present the nascent data regarding the role of hypofractionated (HF) RT in the treatment of the regional lymph nodes. Finally, we will touch on the adoption of HF around the world. Accelerated partial breast irradiation will be presented elsewhere in this issue.

Radiobiologic basis for hypofractionation

In the early history of RT, the use of a few large fractions to treat tumors was common practice. It was quickly noted, however, that these regimens resulted in significant toxicity, which led to the development of conventionally fractionated regimens for the treatment of tumors (7). Specifically in breast cancer, early attempts at HF-WBRT reported very high rates of normal tissue injury, setting back the use of HF regimens (6).

While a detailed explanation of radiobiology is beyond the scope of this review, some basic definitions can help explain the historical context of the decision behind CF-WBRT as well as why HF-WBRT makes sense. In general, the goal of RT is to maximize local control while minimizing late normal tissue toxicity. In order to do this, attributes of both the tumor and the surrounding tissue must be taken into account to predict which dose fractionation regimens will optimize the therapeutic ratio. RT is thought to work through the formation of DNA double strand breaks (DSB), which lead to mitotic catastrophe. DNA DSB can be formed by the less likely event of a single hit breaking both strands leading to cell death (e.g., α kill), or by the more probable event of two single strand breaks happening in close proximity to each other (e.g., β kill). Mathematical models have been developed to describe the intrinsic radiosensitivity of cell types, including both tumors and normal tissues. The most commonly used linear-quadratic model (8,11), though imperfect, has the benefit of describing potential changes in cell survival based on changes in fraction size and total dose. This model describes tissues in terms of an α/β ratio, which describes sensitivity to fraction size, e.g., the lower the α/β ratio, the more curved the cell survival curve will be indicating significant sensitivity to fraction size; the higher the α/β ratio, the more linear the cell survival curve will be indicating minimal sensitivity to fraction size. Fractionation of radiation takes advantage of the differential ability of normal vs. cancer cells to heal, as cancer cells tend to have altered DNA repair mechanisms. Therefore, breaking a course of radiation into pieces can potentially allow normal cells to heal from the radiation in between treatments while the cancer cells would be less likely to do so. By adding multiple fractions together, you can then increase the tumor control probability.

It has long been understood that normal tissues such as subcutaneous fat, lung, and heart have low α/β ratios and are much more susceptible to the effects of higher dose per fraction, which can lead to increased late toxicity. Historically, it was thought that all tumors were insensitive to fraction size based on early laboratory studies of head and neck and cervical squamous cell carcinoma (8). Later experiments in breast cancer cell lines, however, suggested that the α/β ratio of breast cancer may actually be significantly lower (8-10). Therefore, it is not that HFRT would necessarily improve the therapeutic ratio, but rather that there is no benefit to CFRT since breast cancer has a similar α/β ratio to surrounding normal tissue.

These laboratory data led to the development of the first RCT at Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC) comparing HF-WBRT to CF-WBRT, specific design details and clinical outcomes of which are discussed below. This amounted to almost a pure radiobiological HF study in which late toxicity was the primary endpoint and HF-WBRT courses were delivered over the same time period as CF-WBRT, controlling for treatment time as a variable. This study helped to establish a direct estimate of α/β ratio for tumor control of 4.0 Gy (12) and to determine that the α/β ratio of 3 Gy for normal breast toxicity (13). This led to the START (Standardization of

breast radiotherapy) trials initiated by the UK coordinating committee for cancer research. The START A trial had a protocol specified intent to combine the datasets RMH/GOC trial to more precisely estimate the fractionation sensitivity of breast cancer (14). The pooled analysis from these two different studies provides us with our best estimates of the α/β ratio for tumor control (4.6) and late breast appearance (3.4). These clinical studies seemed to support the prior laboratory data suggesting that breast cancer, unlike the better studied squamous cell carcinomas, is in fact sensitive to fraction size. By increasing dose per fraction while simultaneously reducing the total dose, the therapeutic ratio could theoretically be maintained, and as we will show in the below clinical data, may actually be improved.

Clinical trials in support of hypofractionated WBRT

To date there have been five large, prospective randomized phase III studies with long-term follow-up comparing CF-WBRT to HF-WBRT. All but the most recently published study included only patients with invasive carcinoma.

The UK based RMH/GOC study mentioned above was initiated in 1986 and was the first RCT to compare CF-WBRT to HF-WBRT (12,13). It randomized 1,410 patients age <75 years with T1–3N0–1M0 invasive breast cancer who underwent BCS to (I) 50 Gy in 25 fractions, (II) 42.9 Gy in 13 fractions, or (III) 39 Gy in 13 fractions, all delivered over 5 weeks. In this trial, boost was initially part of a second randomization and was subsequently made optional; ultimately 75% of patients received a boost. The primary endpoint was normal tissue change. At 10 years, the 39 Gy arm had slightly worse local recurrence rates (LRR) compared to the 42.9 Gy arm, though it was not statistically different from the CF-WBRT arm. Toxicity outcomes, including photographic and clinical changes in breast appearance and texture as well as shoulder stiffness favored the 39 Gy arm. Distant relapse and survival data were not reported in this study.

Based on the results of the RMH/GOC study, two simultaneous follow-up studies were begun in parallel in 1999: START A and START B. START A was planned extension of the pilot RMH/GOC trial with a stated goal of dose per fraction sensitivity assessment of breast cancer and normal tissue (14). Between 1999 and 2002, 2,236 patients with T1–3aN0–1M0 invasive breast cancer who underwent negative margin resection with or without axillary lymph node dissection (ALND) were enrolled. Patients could undergo lumpectomy or mastectomy without reconstruction. Two of the arms were the same as the RMH/GOC trial (50 Gy in 25 daily fractions and 39 Gy in 13 fractions delivered every other day), but the third arm was replaced with the lower 41.6 Gy in 13 fractions delivered every other day for 5 weeks because of the toxicity seen with the high dose arm from the pilot study. Boost as given in a non-randomized fashion per departmental policy. At 5 years, there was no difference in the primary outcome of locoregional relapse (LRR) for 50 Gy (3.6%), 41.6 Gy (3.5%), or 39 Gy (5.2%). There was no difference in distant relapse or survival at this early time point. The HF 39 Gy arm did show a benefit in regard to cosmesis as rated by late appearance through photographs compared to the CF-WBRT arm. A major shortcoming of both of the START trials is that no estrogen, progesterone, or HER2 status was collected.

The sister START B trial had a more pragmatic design and compared 40 Gy in 15 daily fractions over 3 weeks (a commonly used schedule in the UK at the time) with 50 Gy in 25 daily fractions (15). Inclusion criteria and boost policy matched those for START A. The primary outcomes were locoregional control, late effects, and patient quality of life. At 5 years, there was no difference in LRR (2.2% for 40 Gy *vs.* 3.3% for 50 Gy). Surprisingly, distant relapse, DFS, and OS were better with HF-WBRT, but these differences are unlikely to be due to local tumor control since survival gains would not be expected until 15 years. Cosmesis trended towards favorability for all assessed categories in the HF-WBRT arm, but only reached significance for change in skin appearance (27.8% *vs.* 22.9%).

The START Trialists Group published a 10-year combined analysis of the START A and START B studies (16). LRR remained low between all three arms of START A with only 6.2% of patients having an event. Distant relapse and mortality were similar between the HF-WBRT groups and the CF-WBRT group, but breast induration, telangiectasia, and breast edema all favored the 39 Gy arm as compared to CF-WBRT. START B showed similarly low rates of LRR. The distant relapse and mortality remained stably better in the 40 Gy in 15 daily fractions arm, though this is likely a spurious finding. Breast shrinkage, telangiectasia, and breast edema were all improved in the HF-WBRT compared to the CF-WBRT. Subgroup analysis showed that there was no difference based on age, grade, receipt of boost, or receipt of adjuvant chemotherapy.

The fourth seminal trial of HF-WBRT from NCI Canada started in between the RMH/GOC and START

trials. From 1993 to 1996, 1,234 women with T1–2N0M0 invasive breast cancer who underwent lumpectomy and axillary dissection with negative margins were randomized to 50 Gy in 25 daily fractions or 42.5 Gy in 16 daily fractions (17,18). Eleven percent of patients received chemotherapy and 41% received tamoxifen. As with the other trials, receptor status was not part of inclusion criteria. There was no difference in local recurrence, DFS, or OS at 5 or 10 years. Good or excellent cosmesis at 10 years was also equivalent in the CF-WBRT (71.3%) and HF-WBRT (69.8%) arms. The authors noted that there were no excess cardiac deaths in the HF arms. Unplanned subset analysis suggested that there may be increased local recurrence with HF-WBRT in patients with high-grade tumors (15.6% *vs.* 4.7%). Subsequent criticism of the finding centered on the use of the older Scharff bloom Richardson grading system. After central pathologic review using the Nottingham grading system, this difference washed out (19). This, along with the fact that no other trial showed a difference in high-grade tumors, has led to the conclusion that tumor grade should not be a determinant of fractionation.

The 9-year results of the Danish Breast Cancer Group (DBCG) HYPO trial, which included patients with early-stage breast cancer and DCIS were published this year (20). A total of 1,854 patients enrolled from 2009 to 2014 were randomized to 50 Gy in 25 fractions *vs.* 40 Gy in 15 fractions. Nine-year LRR was 3.3% in the CF-WBRT group and 3.0% in the HF-WBRT group, not statistically different. Induration was numerically better for the hypofractionation group, though it did not reach significance. Other toxicities including telangiectasia, changes in pigmentation, edema, and pain were equivalent with low rates in both groups. Cosmesis and patient satisfaction were excellent and high in both groups. Cardiac and lung toxicity rates were extremely rare and did not differ between groups. Thirteen percent of enrolled patients had DCIS, and there were no differences in LRR in this subgroup.

We await the results of the TROG 07.01 trial which will provide the definitive evidence of clinical equipoise for HF-WBRT for the treatment of DCIS (21). Extrapolating from the invasive data, currently, HF-WBRT is widely adopted in the treatment of DCIS.

Clinical trials assessing hypofractionated RT in the postmastectomy and regional nodal irradiation setting

While major rigorous randomized trials are ongoing right now, the idea of using hypofractionated regional nodal irradiation (HF-RNI) or postmastectomy radiation therapy (HF-PMRT) is not new. In fact, the original DBCG PMRT trial used hypofractionation with 36 Gy in 12 fractions (6), though with significantly increased toxicity. Similarly, the PMRT trial out of British Columbia, which randomized node positive patients to chemotherapy alone *vs.* chemotherapy with PMRT including the chest wall and regional lymph node regions (axillary, supraclavicular, and internal mammary nodes), actually used a HF-PMRT regimen of 37.5 Gy in 15 fractions (22). This trial was one of the first to show not only a locoregional control, but also a survival benefit, for radiation in the post mastectomy setting, though long-term toxicity was not reported. In addition, 21% of patients in the RMH/GOC trial, 14% of patients in START A, and 7% of patients in START B received regional nodal irradiation (12-16). The long-term follow-up of the START studies reported no significant increase of shoulder stiffness or arm lymphedema in the HF arms, and there was only one case of brachial plexopathy recorded across both trials (16).

The only phase III RCT of HF-PMRT *vs.* CF-PMRT published to date is from Chinese Academy of Medical Sciences (23). This study included patients with advanced disease, having at least four positive axillary lymph nodes or primary tumor stage T3–4, all of whom underwent mastectomy and ALND. A total of 820 patients were randomized to receive CF-PMRT (50 Gy in 25 fractions) or HF-PMRT (43.5 Gy in 15 fractions). Five-year LRR was non-inferior in the HF-PMRT group (8.1%) as compared to the CF-PMRT group (8.3%). Grade 3 acute skin toxicity was improved in the HF-PMRT group (3% *vs.* 8%), and there were no other reported differences in acute or late toxicity. Importantly, reconstruction was not allowed, and most patients were planned using older two-dimensional techniques. Longer follow-up will be important as the late cardiac effects are unlikely to manifest until 10 years post-treatment, and these results will need to be evaluated in the context of older planning techniques.

A recently published phase II multi-institutional single arm study used HF-PMRT delivered as 36.63 Gy in 11 fractions followed by an optional scar boost of 12.32 Gy in 4 fractions in women with stage II–IIIA breast cancer (24). The 5-year results demonstrated a low complication rate with excellent tumor control on par with historical controls (25). This study served as the basis of the ongoing ALLIANCE A221505 "RT CHARM" trial phase III RCT comparing CF-PMRT (50 Gy in 25 fractions) to HF-PMRT (42.5 Gy in 16 fractions) in women with node

positive, stage II–IIIA invasive breast cancer in whom immediate or delayed reconstruction is planned. This trial allows for neoadjuvant and adjuvant chemotherapy. Scar boost is not allowed. The primary outcome of this trial is reconstruction complication rate, with tumor control and other toxicity outcomes as secondary endpoints. RT CHARM along with the similarly designed FABREC study, which requires immediate reconstruction, will give us more definitive information on the safety and efficacy of HF-PMRT in women undergoing reconstruction.

Ultra-hypofractionation randomized trials

After the first-generation trials showed HF-WBRT was non-inferior to CF-WBRT the next frontier was to pursue highly compressed schedules. The UK FAST trial ran from 2004 to 2007 and randomized 915 patients to 50 Gy in 25 fractions *vs.* 30 Gy in 5 fractions *vs.* 28.5 Gy in 5 fractions (26,27). The five fraction regimens were delivered once a week to prevent time from being a confounding variable, similar to the pilot RMH/GOC study. Eligibility criteria included: age ≥50 years, invasive carcinoma, pT1–2 (size <3 cm), pN0 after lumpectomy. Eighty-eight-point-four percent patients were intended to receive endocrine therapy. The primary endpoint was photographic change in breast appearance with local control as a secondary endpoint. Assessment of acute skin toxicity showed grade ≥3 reaction highest in the 50 Gy in 25 fractions (10.9%) *vs.* 2.7% (30 Gy in 5 fractions) *vs.* 1.9% (28.5 Gy in 5 fractions) (26). At 5 years 79.5% of patients had no change photographic breast appearance (26,27). The 30 Gy arm had statistically more mild/moderate change in breast appearance at 5 years compared to CF-WBRT (P<0.019). Physician assessed normal tissue effects showed moderate/marked breast shrinkage was the most prevalent side effect at 5 and 10 years. Furthermore, moderate/marked normal tissue effect was 10% higher in 30 Gy arm when compared to 50 Gy (P<0.001) at 5 years (27). This result was consistent at 10 years and estimated moderate/marked normal tissue effect for 30 Gy arm was 9% higher when compared to 50 Gy and statistically significant. It was not statistically different when comparing 28.5 to 50 Gy treatment arms. The authors concluded that 28.5 Gy in 5 fractions was comparable to 50 Gy in 25 fractions radiobiologically for normal tissue toxicity, but normal tissue effects were higher for 30 Gy in 5 fractions. This trial was not designed to determine ipsilateral breast tumor recurrence (IBTR) rates between treatment arms, but the 10-year update of the trial revealed a low total IBTR of 1.2% (27).

The FAST-Forward study had a pragmatic design and was a phase 3, non-inferiority trial comparing five-fraction, 1 week adjuvant radiation schedule to standard 15 fraction schedule delivered over 3 weeks (28). From 2011 to 2014, 4,110 patients were randomized to one of three treatment schedules: 40 Gy in 15 daily fractions *vs.* 27 Gy in 5 fractions *vs.* 26 Gy in 5 fractions to the whole breast or chest wall. Patients underwent either breast conservation or mastectomy and axillary surgery via either SLNB or ALND. Axillary radiation was not allowed on this study. Eligible patients were ≥18 years with pT1–3, pN0–1, M0 breast cancer. A trial amendment was passed in 2013 which excluded favorable patients: ≥65 years old, pT1, grade 1–2, ER positive, and HER2 negative from enrollment. Concurrent endocrine therapy and trastuzumab was allowed, but concurrent chemotherapy was excluded.

After median follow up of 71.5 months, IBTR rates were 2.1% (40 Gy in 15 fractions) *vs.* 2% (27 Gy in 5 fractions) *vs.* 1.5% (26 Gy in 5 fractions) (28). The estimated absolute difference in IBTR when compared to 40 Gy were –0.3% for 27 Gy arm and –0.7% for 26 Gy arm, meeting the non-inferiority threshold for both arms.

FAST-Forward conducted two substudies to determine the impact of fraction size on acute toxicity (29). The trialists aimed to describe any grade ≥3 toxicity 4 weeks after treatment completion in any of the trial arms. In the first substudy, acute grade ≥3 toxicity with 40 Gy/15 fractions was 13.6% *vs.* 27 Gy/5 fractions was 9.8% *vs.* 26 Gy/5 fractions was 5.8%. Of these patients, 29 had undergone a boost and there was no difference in acute toxicity with the addition of boost for any treatment arm. In the second substudy, which excluded patients receiving tumor bed boost, acute grade >3 toxicity is as follows: 40 Gy/15 fractions was 0% *vs.* 27 Gy/5 fractions was 2.4% *vs.* 26 Gy/5 fractions was 0%. At 5 years physician assessed moderate to marked normal tissue effect was 9.9% in the 40 Gy arm *vs.* 15.4% in the 27 Gy arm *vs.* 11.9% in 26 Gy arm (28). These findings were statistically significant when comparing 40 to 27 Gy (P=0.0003), but not for 40 *vs.* 26 Gy. Furthermore, normal tissue effects were significantly higher for the 27 Gy arm when compared to the 26 Gy arm (P=0.0001).

ASTRO consensus statement

In 2011, ASTRO published consensus guidelines on whole breast radiation fractionation (30). The task force

Table 1 Hypofractionation and ultra-hypofractionation randomized trials inclusion criteria

Variable	RMH/GOC (12,13)	START A (14,16)	START B (15,16)	NCI Canada (17,18)	DBCG HYPO (20)	UK FAST (26,27)	UK FAST-Forward (28)
Stage	pT1–3N0–1	pT1–3aN0–1	pT1–3aN0–1	pT1–2N0	pTis–2N0–1mic	pT1–2, pN0	pT1–T3, pN0–1
N (number of patients)	1,410	2,236	2,215	1,234	1,854 (1,608 invasive)	915	4,110
Median follow-up	9.7 years	9.3 years	9.9 years	12 years	7.26 years	9.9 years	5.96 years

RMG/GOC, Royal Marsden Hospital and the Gloucestershire Oncology Centre; START, UK Standardisation of Breast Radiotherapy (START); NCI Canada, National Cancer Institute of Canada; DBCG HYPO, Danish Breast Cancer Group Hypofractionation; UK FAST, United Kingdom FAST Trial; UK FAST-Forward, United Kingdom FAST-Forward Trial.

concluded that patients meeting the following criteria has no difference in outcomes from CF-WBRT *vs.* HF-WBRT: age ≥50, pT1–2 after BCS, no chemotherapy, and dose inhomogeneity of ±7% at central axis. After the publication of these guidelines long term data for the START trials was published. ASTRO updated the guidelines in 2018 to broaden the criteria for patients getting HF-WBRT (31). The task force recommended that HF-WBRT should be the standard for patients undergoing WBRT without RNI with preferred dose fractionation of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions to treat the breast and low axilla with or without a tumor bed boost. Moreover, the updated guidelines supported the use of HF-WBRT for patients of any age, any tumor size, any systemic therapy, or breast size with acceptable dose homogeneity.

Adoption of hypofractionation

Although ASTRO consensus guidelines and multiple randomized trials support the use of HF-WBRT in early-stage breast cancer; adoption has not been robust in the United States. In light of this, in 2013/2014 ASTRO introduced the "Choosing Wisely" campaign which highlighted HF-WBRT should be considered in women >50 years with early-stage breast cancer (32). Delayed adoption of HF-WBI is also related to limited data on acute toxicity. Shaitelman et al. and Schmeel et al. conducted two randomized, multicenter trials demonstrating lower acute toxicity with HF-WBI when compared to CF-WBI (33,34). These studies helped bridge acute toxicity fears of HF-WBI. Encouragingly, a recent National Cancer Database analysis shows an increase in utilization HF-WBI from 20.9% in 2012 to 59.0% in 2016 (35). In Canada, after the publication of Ontario trial the utilization of HF-WBRT rose to 70% for early-stage breast cancer patients (18,36). Similarly, adoption of HF-WBRT is close to >75% in

the UK while conventional fractionation is utilized more regularly in other European countries (37). Conversely, after similar guidelines, New South Wales population-based study shows that 45% patient meeting eligibility criteria receive HF-WBRT (38). While the study did find that utilization of HF-WBRT did increase from 37% in 2008 to 48% in 2012, the majority of patients still received CF-WBRT.

Conclusions

The evolution in the treatment of breast cancer has included the development of BCT as a standard in early-stage breast cancer. The standard has been daily radiation treatment delivered over the course of 5–7 weeks. Randomized trials now definitively support the use of HF-WBRT in the majority of patients allowing women to completed treatment quickly with comparable outcomes (*Table 1*). Ultra-hypofractionated courses may represent the next frontier, though follow-up remains short (*Table 1*). In light of the global COVID-19 pandemic, shorter courses are being adopted out of necessity. Once week schedules allow for treatment completion with decreased time of exposure to healthcare facilities. This pandemic may serve as an impetus for increased adoption of HF-WBRT and as a natural prospective study of the multitude of patients getting ultra-hypofractionated courses.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (William Small Jr. and Parul Barry)

for the series "Advancements and Opportunities for Breast Irradiation" published in *Annals of Breast Surgery*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/abs-20-128). The series "Advancements and Opportunities for Breast Irradiation" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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