A Brief Insight about Hypofractionated Whole Breast Irradiation

Nehal Gamal El-Sayed Mohamed, Maher A. Aidarous, Mohammed W. Hegazy, Amira Elwan

Clinical Oncology Department, Faculty of Medicine - Zagazig University, Egypt

Email: nonojemmy44@gmail.com, NGelsayed@medicine.zu.edu.eg

Abstract

Background: When treating early breast cancer, hypofractionated whole breast irradiation (HF-WBI) has been shown to be effective, safe, and even better in terms of late or acute radiation harm. In addition to these benefits to the patient, the healthcare system as a whole stands to reap savings from this innovation as well. In this review, we looked at the most important randomised trials of HF-WBI, paying special attention to the radiobiologic aspects of HF-WBI and how they relate to its implementation in clinical settings, as recommended by the American Society for Therapeutic Radiology and Oncology (ASTRO) guideline. The global national health insurance service system necessitates more research to determine the existing practise pattern or cost effectiveness.

Keywords: Hypofractionated Whole Breast Irradiation

Introduction

Whole breast irradiation after breast conserving surgery (BCS) has been established as the standard treatment for breast cancer. The radiation schedule of 50 Gy/25 fractions in 5 weeks used in earlier trials demonstrated the efficacy of BCS and adjuvant whole breast radiotherapy to be equivalent to that of mastectomy [1,2]. The support of standard fractionated whole breast irradiation (SF-WBI) for breast cancer is based on the radiobiologic consideration that radiation damage to normal tissue is greater with larger fraction size without additional tumor control [3]. As a result, SF-WBI in the adjuvant treatment after lumpectomy has been the standard for several decades. However, some of the challenges of SF-WBI are cost and inconvenience of the patient involved with daily treatment courses from 5 to 7 weeks. This has led to the suggestion of short fractionation as a new standard following BCS for early stage breast cancer. Hypofractionated whole breast irradiation (HF-WBI), based on precedent studies over the past two decades, offers an opportunity for improved patient convenience, lower healthcare costs, and greater access to care without sacrificing treatment outcomes.

Key Randomized Trials

Up until now, 4 randomized trials—the Royal Marsden Hospital/Gloucestershire Oncology Center (RMH/GOC) trial [4,5], the UK Standardisation of Breast Radiotherapy (START) trial A and B [6-8], and the Canadian trial [9]—have supported the establishment of HF-WBI with recent publication of 10-year outcomes. All studies included stage T1-3 and N0-1 early breast cancer. The majority of patients were older than 50 and some proportion of the patients received chemotherapy. Though allowed in other trials, the Canadian trial did not include regional nodal irradiation and tumor bed boost.

The radiobiologic rationale for HF-WBI is based on the notion that if α/β of the tumor is similar to the α/β of irradiated normal tissue, larger fraction sizes will be more effective without giving a detrimental effect to normal breast tissue. In such context, the RMH/GOC trial was a pilot study to identify the α/β of breast tissues, using late normal tissue effects as the primary endpoint. The RMH/GOC trial compared 2 different HF-WBI schedules, 39 Gy and 42.9 Gy in 13 fractions over 5 weeks, with the standard 50 Gy/25 fraction schedule. Comparing 3 different regimens allowed the estimation of α/β for several radiation-related

endpoints by assuming linearity between the 2 test dose levels. The 13-fraction schedule that is isoeffective with 50 Gy in 25 fractions can be determined by interpolation [4]. After a minimum follow-up 9.7 years, any change in breast appearance was seen in 39.6%, 30.3%, and 45.7%, and ipsilateral breast tumor relapse (IBTR) occurred in 12.1%, 14.8%, and 9.6% for the 50 Gy/25 fraction, 39 Gy/13 fraction, and 42.9 Gy/13 fraction regimen, respectively [4]. Based on these results, α/β for breast cancer was estimated to be 4.0 Gy, which is similar to that of late-reacting healthy tissue [5]. Because 42.9 Gy/13 fractions seemed to have slightly more late normal tissue effects than standard fractionation [6], START A trial compared 39 Gy and 41.6 Gy with 13 fractions over 5 weeks with standard fractions. It should be noted that the patients treated with the HF-WBI schedule in the RMH/GOC and START A trials were treated with total treatment time maintained to 5 weeks, which means these patients were not treated daily.

At 10-year follow-up, START A trial showed no significant difference between the HF-WBI arms (39 Gy and 41.6 Gy) and the SF-WBI control arm. Disease free survival and overall survival were not significantly different between any of the START A treatment schedules [8]. Moreover, moderate or marked breast induration, telangiectasia, and breast edema were significantly less common normal tissue effects in the 39 Gy group than in the 50 Gy group [8].

START trial B aimed to provide a robust evidence base for clinical practice in breast radiotherapy by comparing a commonly used 40 Gy/15 fractions HF-WBI schedule within 3 weeks with SF-WBI. There was no difference between the 2 treatment arms for the primary end point of locoregional failure. For the late normal tissue, breast shrinkage, telangiectasia, and breast edema were significantly less common in the HF-WBI than in the SF-WBI group [8].

Lastly, in the Canadian trial, HF-WBI 42.5 Gy/16 fractions daily treatment was compared with SF-WBI. There was no difference in cumulative local recurrence between the 2 dose schedules at 10 years [9]. Local recurrence was 6.7% in SF-WBI arm and 6.2% in HF-WBI arm. Regarding cosmetic outcome, 71.3% of patients in SF-WBI arm and 69.8% of the patients in HF-WBI arm had a good or excellent cosmetic outcome without statistically significant difference.

ASTRO Guideline

Based on these studies, ASTRO published an evidence-based guideline for HF-WBI in 2011 [10]. The guideline states that the panel reached a consensus on supporting HF-WBI for patients who meet all of the following criteria: age older than 50 years, stage T1-2N0 disease, no use of chemotherapy, and central axis dose of 93% to 107%. Recommended dose-fractionation schemes are 42.5 Gy in 16 fractions as in the Canadian trial, 41.6 Gy in 13 fractions over 5 weeks as in START A, and 40 Gy in 15 fractions over 3 weeks as in START B. The HF-WBI doses used in the RMH/GOC trial, compared with the 50-Gy arm, were not recommended because the 42.9-Gy arm yielded excessive toxicity and the 39-Gy arm yielded a higher risk of IBTR.

This criteria is based upon the inclusion criteria and outcomes of the key studies stated above. These recommendations are relatively conservative. The guideline states that "for other patients, the task force could not reach agreement either for or against the use of HF-WBI, which nevertheless should not be interpreted as a contraindication to its use [11]."

Indication beyond the Guideline

1. Age

Younger age is a risk factor for local failure of breast cancer [12]. However, only 21%–30% of the patients in the key randomized trials of HF-WBI were younger than 50 years. Subgroup analysis in the Canadian trial showed that the influence of fraction schedule on IBTR was not different regardless of age. Moreover, in 10-year follow-up results of the START trials published after the ASTRO guideline, younger age patients favors HF-WBI in terms of local-regional relapse [8]. This justifies the implication of hypofractionation for patients younger than 50 years.

2. Ductal carcinoma in situ (DCIS)

DCIS patients were not included in major studies. However, there is an ongoing randomized trial to test the efficacy and safety of HF-WBI for patients with DCIS [13]. Moreover, there are numerous retrospective data and meta-analysis that found no difference in local recurrence between the HF-WBI and SF-WBI

[14,15]. HF-WBI for DCIS is unlikely to lead to worse tumor control or worse side effect compared with SF-WBI [11]. Therefore, HF-WBI could be offered as an option to patients.

3. Grade

In the Canadian study, subgroup analysis showed that hypofractionation appeared to be less effective for high-grade tumors than for lower-grade tumors [9]. In contrast, recent 10-year follow-up results of START A and B did not demonstrate treatment effect to be significantly different respective to grade [8]. This discrepancy could be explained by the fact that tumor bed boost was not allowed in the Canadian study, whereas 61% and 39% of the patients received tumor bed boost with 10 Gy in 5 fractions in START A and B trials, respectively. Another explanation comes from the fact that the grading system originally conducted in the Canadian trial was the Scharff Bloom Richardson (SBR) grading system. This system was replaced by the more quantitative and reproducible Nottingham grading system. After a central pathology review and assessment of tumor grade using the Nottingham grading system, the tumor grade did not show relation to the type of radiotherapy (RT) received in terms of local recurrence [16]. Moreover, there is a population-based cohort study showing no inferior outcome of hypofractionation in patients with grade 3 breast cancer [17].

4. Regional node irradiation (RNI)

Only 21%, 14%, 7%, and 0% of the patients received regional nodal irradiation in RMH/GOC, START A, START B, and Canadian trials, respectively. Although only 1 of 750 patients in the 41.6 Gy/13 fraction arm in the START A trial developed brachial plexopathy [6], and there were no significant difference of shoulder stiffness or arm edema between HF-WBI and SF-WBI arms in START A and B trials [8], the follow-up after HF-WBI in both START trials was not considered sufficient to exclude such late toxicity. However, there were several retrospective data reassuring the use of hypofractionation in RNI. Based on the literature review by Galecki et al. [18], the risk of radiation-induced brachial plexopathy was less than 1% when using regimens with dose per fraction between 2.2 Gy and 2.5 Gy with total dose between 34 Gy and 40 Gy. Contemporarily, published data support the feasibility of hypofractionated RNI and the need for a prospective randomized trial addressing clinical outcomes and toxicity of hypofractionated RNI compared with those of standard fractionation RNI [19].

5. Chemotherapy

In the key randomized trials, 11% to 35% of the patients used chemotherapy. Anthracycline and taxane containing chemotherapy regimens were used in 25% and 1%, respectively, for patients in the START A trial and in 13% and 0.4%, respectively, for patients in the START B trial [6,7]. Major concern regarding anthracycline chemotherapy is cardiac toxicity. Hazard ratios for normal tissue toxicity were not significantly different regardless of use of chemotherapy in the subgroup analyses of Canadian and START trials [8,9]. Although current follow-up data is relatively short considering late cardiac toxicity, radiobiologic consideration of HF-WBI, which will be described in detail later, and modern radiation delivery techniques such as intensity modulated radiotherapy (IMRT) may save substantial dose to the heart.

6. Boost

Regarding tumor bed boost, 75% received 14 Gy/7 fractions in RMH/GOC trials and 61% and 39% received 10 Gy/5 fractions in the START A and B trials, respectively, whereas no patients were given boost irradiation in the Canadian trials. ASTRO guideline stated that “the task force agreed that the use of HF-WBI alone (without a boost) is not appropriate when a tumor bed boost is thought to be indicated. The optimal HF-WBI regimen to use when a boost is given and the optimal tumor-bed boost dose-fractionation to use in conjunction with HF-WBI have not been determined.” However, the meta-analysis of RMH/GOC, START A, and START B found that for any moderate or marked physician-assessed normal tissue effects in the breast significantly favored the HF-WBI arms regardless of tumor bed boost. It is noteworthy that the ASTRO guideline was published in 2011, before this most recent data became available [8]. Kim et al. [20] reported the results of a phase II trial of HF-WBI with 39 Gy in 13 fractions of 3 Gy to the whole breast once daily over 5 consecutive working days, and 9 Gy in 3 sequential fractions of 3 Gy to the lumpectomy cavity, all within 3.2 weeks. They reported excellent disease control and tolerable skin toxicity in patients

with early-stage breast cancer. National Comprehensive Cancer Network (NCCN) guidelinestates that“ a boost is recommended in patients at higher risk for recurrence with doses of 10–16 Gy in 4–8 fractions.”

Radiobiologic Consideration

As abovementioned, a significant accomplishment from the RMH/GOC and START A trials is that fractionation sensitivity could be evaluated; α/β of the breast tumor and normal tissue. These values could vary according to the outcome measurement and follow-up periods, as listed in Table 2. Along with the RMH/GOC trial, Yarnold et al. [4] reported that α/β is 4.0 for local control and 3.6 for adverse effects. After a 5 year outcome of the START A trial, a meta-analysis with RMH/GOC and START A trial showed that the adjusted estimates of α/β value was 4.6 Gy for tumor control and was 3.4 Gy for late change in breast appearance (photographic) [6]. Finally, the meta-analysis of RMH/GOC and START A trial after the 10-year outcome of the START trial provided an adjusted α/β value of 3.5 Gy for local regional relapse [8] and 3.1 Gy for adverse effects [21].

Another important aspect of HF-WBI irradiation is that the irradiated total dose in HF-WBI calculated in EQD2 is slightly reduced than that of standard fractionation (Table 1). Yarnold et al. [22] pointed out that the curve of normal tissue toxicity in the dose-response graph ought to be steeper than the curve for subclinical breast tumor control based on the fact that local control would be around 70% without radiation whereas normal tissue toxicity would be zero without radiation. Hence, this leads to small decrease in total dose while allowing greater decrease in normal tissue toxicity under the acceptable compromise of local control (Fig. 1)

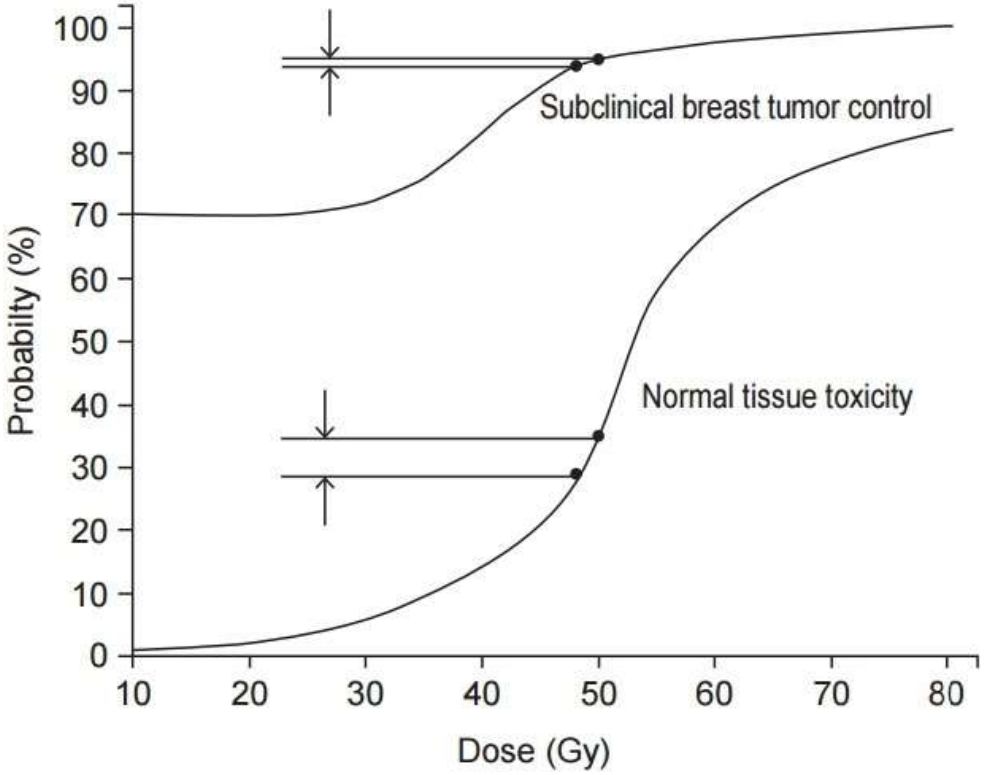

Fig. 1.

Dose-response curve for subclinical breast tumor control and normal tissue toxicity. Yarnold et al. [22] mentioned that small decrease in total dose allows greater decrease in normal tissue toxicity under the acceptable compromise of local control considering different steepness of the two curves.

Major concern when using larger fraction size is cardiac toxicity. In contrary to common belief that hypofractionation has a harmful effect on the heart, it is noteworthy to remember that EQD2 of the hypofraction schedule is gentler to the heart than conventional fractionation. Even if we regard α/β of the heart as an extreme value (i.e., α/β = 1), the mean EQD2 dose to the heart in the hypofraction schedule of the Canadian trial (42.5 Gy/16 fractions) has a lower value than that of the conventional schedule [23].

While key studies focused on the late normal tissue effect concerning greater fraction size, reports on acute reaction with hypofractionation were published recently [24-26]. Because the total dose of hypofractionation is slightly lower than conventional radiation, the acute skin reaction is expected to be much reduced considering the higher value of α/β for acute skin reaction. As expected, Jagsi et al. [25] reported that patients with hypofraction had lower physician-assessed skin reaction, self-reported pain, bothersome burning, bothersome pain, bothersome swelling and fatigue. Shaitelman et al. [26] also reported lower acute toxic effects and associated better quality of life for patient with hypofraction. These studies confirmed that HF-WBI provided patients with more convenience (from the shorter treatment schedule) and reduced acute dermatitis and pain which eventually improved quality of life.

Further Consideration

HF-WBI using 15–16 daily treatments has become widely accepted in parts of Canada and the UK, but in other country, i.e., USA, HF-WBI after BCS has been adopted more slowly [27]. Economic realities of a fee-for-service system may have contributed to such slow adoption of this technique. As part of the 'Choosing Wisely' campaign by American Board of Internal Medicine, which is intended to avoid wasteful or unnecessary medical cost, ASTRO released a list containing the following statement: "Don't initiate whole breast radiotherapy as a part of breast conservation therapy in women age >50 years with early stage invasive breast cancer without considering shorter treatment schedules." With this effort, adoption of hypofractionation is increasing in the USA [28-30].

Conclusion

HF-WBI has been proved its effectiveness and safety. The 50 Gy in 25–28 fractions prescription does not have the advantage of convenience for patients nor the advantage of a reduced biological effectiveness associated with the 'extended' fractionation schedule. HF-WBI shows even better late or acute radiation toxicity for early breast cancer. Further investigation to identify the current practice pattern or cost effectiveness is warranted under the national health insurance service system. In our view, HF-WBI could be new standard for whole breast radiotherapy in early breast cancer after BCS.

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