



Progress of clinical study on hypofractionated radiotherapy after breast-conserving surgery

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Abstract: Whole-breast radiotherapy after breast-conserving surgery (BCS) can improve patient survival while reducing local tumor recurrence. Although standard breast radiotherapy can achieve good tumor control and cosmetic effects with low toxicity, the 5- to 7-week treatment time is relatively long for patients and can result in wasted medical resources. Therefore, there is a growing trend toward hypofractionated radiotherapy (HFRT), which accelerates partial-breast irradiation. Both short-course radiotherapy and conventional fractionated radiotherapy are safe and effective treatment modes, with similar survival and local tumor control effects as those of conventional radiotherapy (CRT), and adverse reactions can be tolerated. Compared with conventional fractionated radiotherapy, short-course radiotherapy saves medical resources and has a shorter total treatment time, reduced treatment costs, and an improved quality of life for patients.

Keywords: Breast cancer; breast-conserving surgery (BCS); whole-breast irradiation (WBI); hypofractionated radiotherapy (HFRT); partial-breast irradiation

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Introduction

Breast cancer is the most common cancer among women, and the 2019 American Cancer Statistics Report showed that breast cancer accounted for 30% of all new cancer cases in women (1). At present, breast-conserving surgery (BCS) is the most common treatment for early breast cancer (EBC). Whole-breast irradiation (WBI) after BCS has an overall survival rate equivalent to that of modified radical mastectomy (2). A meta-analysis of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed 10-year recurrence rates of 19.3% vs. 35.0% and 15-year breast-related mortality reductions of 21.4% vs. 25.2%, respectively, in patients who underwent BCS and received WBI compared with those who did not receive WBI (3). Although conventional fractionated WBI (CF-WBI) has good tumor control and fewer adverse reactions, long-term

hospitalization brings great psychological and economic burdens to patients. When promoting BCS to patients, although postoperative adjuvant radiotherapy can reduce local recurrence and mortality, 21% of patients refuse to receive radiation therapy (4), and even EBC patients with early breast-conserving indications choose mastectomy to avoid radiotherapy. In recent years, as radiotherapy technology has advanced, hypofractionated WBI (HF-WBI) and accelerated partial-breast irradiation (APBI) have been receiving increasing attention. This article reviews the research progress regarding HF-WBI after BCS.

Biological basis of hypofractionated radiotherapy (HFRT) for breast cancer

HF-WBI involves increasing a single dose (>2 Gy) and reducing the total number of treatments and radiation

doses, thus shortening the total treatment time while ensuring an equivalent or increased equivalent biological dose of CF-WBI. The radiosensitivity of the tissue is expressed as an α/β value, and as the α/β value decreases, the tissue radiosensitivity increases compared with that of the single larger fractionated dose. If cells in the early-reacted tissues are renewed quickly, the α/β value will be high and the lesions will appear early after radiotherapy. The cells in the late-reactive tissues will update slowly, and the α/β value will be low and the lesions will appear very late after radiotherapy. Owen *et al.* (5), Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC) trial results showed that a single dose of the radiosensitivity α/β value of breast cancer is approximately 4.0 Gy, similar to the α/β value of normal breast tissue. Yarnold *et al.* (6) found that a single α/β dose for normal breast tissue is approximately 3 Gy, and the α/β value of breast cancer is low. Radiobiologically, HF-WBI can guarantee a curative effect and does not increase the radiotherapeutic damage to the late-reacting tissue.

Hypofractionated WBI after BCS

Efficacy

Several randomized trials and meta-analyses (5,7-11) have shown that HF-WBI is safer and more effective than CF-WBI after BCS in most patients with EBC. In the RMH/GOC trial, Owen *et al.* (5) randomized 1,410 patients with BCS into 50.0 Gy/25F, 39.0 Gy/13F, and 42.9 Gy/13F groups, and the 10-year ipsilateral tumor recurrence rates were 12.1%, 14.8%, and 9.6%, respectively. In the START trial, Haviland *et al.* (7) enrolled patients with pT1-3a, pN0-1, and M0 breast cancer. This trial was divided into the 41.6 Gy/13F, 39.0 Gy/13F, and 50.0 Gy/25F groups, and the 41.6 and 50.0 Gy groups had 10-year local recurrence rates of 6.3% and 7.4%, respectively. The B trial was divided into the 40 Gy/15F and 50 Gy/25F groups, which had 10-year local recurrence rates of 4.3% and 5.5%, respectively. In a Canadian trial, Whelan *et al.* (8) randomly divided 1,234 BCS patients into the CF-WBI group at 50.0 Gy/25F for 35 days and the HF-WBI group at 42.5 Gy/16F for 22 days. The 10-year local recurrence rates of the two groups were 6.7% and 6.2%, respectively, and the HF-WBI results were not inferior to the CF-WBI results. The ASTRO guidelines reported by Smith *et al.* (12) determined that the applicable patient population for HF-WBI was those aged ≥ 50 years, with pT1-2, N0, BCS and no chemotherapy.

HF-WBI at 42.5 Gy/16F is recommended for patients who have never received a tumor bed boost. Herbert *et al.* (9) compared 1,335 cases of T1-T2, N0, and M0 breast cancer patients who had undergone HF-WBI (42.5–44 Gy/16F; n=1,083) or CF-WBI (45–50 Gy/25F; n=252) after local disease control. The local recurrence rates at 10 years did not differ between patients who underwent HF-WBI and those who underwent CF-WBI (6.9% vs. 6.2%, P=0.99), suggesting that HFRT is not inferior to conventional fractionated radiotherapy. In 2013, the ASTRO Choosing Wisely campaign recommended low-fractionation for patients aged ≥ 50 years with early-stage breast cancer to avoid routine use of intensity-modulated radiation therapy for WBI, further recommending the long-term safety and clinical effectiveness of HF-WBI (13). Janssen *et al.* (10) studied 98 patients who underwent BCS and received 41.6 Gy/13F + a tumor bed boost of either 9 Gy/3F or 12 Gy/4F. The median follow-up was 28 months. Patients' local control rate, local regional control rate, disease-free survival rate, and overall survival rate were 100%, 100%, 98%, and 96%, respectively, and the tumor control was satisfactory, suggesting that the HFRT was effective. Valle *et al.* (11) included 13 randomized trials in a meta-analysis of 8,189 patients with T1-T2 and/or N1 breast cancer or carcinoma in situ after BCS and found that compared with conventional fractionation, HFRT did not reduce the local control rate of the disease (RR 0.97; 95% CI, 0.78–1.19). As an important risk factor for breast cancer recurrence, younger women were not represented in the trial, and most trials did not indicate the survival rate. The application of HFRT in young women remains controversial. Shaikh *et al.* (14) analyzed 348 patients with BCS aged < 50 years and found a median follow-up time of 66.9 months, a 3-year overall survival rate of 99.6%, a disease-free survival rate of 96.3%, and a local recurrence-free survival rate of 97.7%, suggesting that HFRT was safe and effective for patients < 50 years old. On this basis, ASTRO Clinical Guidelines for Whole Breast Radiotherapy [2018] further expanded the applicable patient population for HF-WBI and considered that age, tumor grade, and chemotherapy were not contraindications for HF-WBI (15). The European Society of Oncology (ESMO) guidelines recommend HFRT as a routine postoperative radiotherapy for breast cancer (15–16 times, at ≤ 3 Gy each time) (16).

Adverse reactions and cosmetic effects

The advantage of breast-conserving treatment is that

it better preserves the shape of the breast and improves cosmetic effects. HF-WBI also has a good cosmetic effect compared with that of CF-WBI, and its adverse reactions can be tolerated. In the RMH/GOC trial, Owen *et al.* (5) evidenced that the efficacy and adverse effects were similar in the 39.0 Gy/13F group compared with those of the 42.9 Gy/13F and the 50.0 Gy/25F groups. The results of the START A trial found significantly less moderate or severe breast induration, telangiectasia, and breast edema in the 39.0 Gy/13F group than in the 50.0 Gy/25F group, and adverse reactions in the normal tissue did not significantly differ between the 41.6 Gy/13F group and the 50.0 Gy/25F group. The START B trial showed that moderate breast contraction, telangiectasia, and breast edema were significantly lower in the 40 Gy/15F group than in the 50 Gy/25F group. HF-WBI achieved good cosmetic results with no increase in adverse reactions in normal tissues (7). The Canadian trial by Whelan *et al.* (8) had a median 12-year follow-up time and showed excellent rates for the cosmetic effects of both CF-WBI and HF-WBI at 10 years (71.3% *vs.* 69.8%, respectively).

Shaitelman *et al.* (17) found that the overall incidence of acute adverse reactions with grade ≥ 2 was lower in the HF-WBI group than in the CF-WBI group (47% *vs.* 78%, respectively, $P < 0.001$), and the HF-WBI group experienced a low degree of moderate fatigue and an improved quality of life compared with that of the CF-WBI group ($P = 0.06$). Jagsi *et al.* (18) found a higher incidence of adverse skin reactions in the CF-WBI group than in the HF-WBI group, including moist desquamation (28.5% *vs.* 6.6%, respectively, $P < 0.001$) and dermatitis graded 2 or higher (62.6% *vs.* 27.4%, respectively, $P < 0.001$). Swanick *et al.* (19) compared BCS patients with clinical stage 0–II breast cancer, who were divided into the 50.00 Gy/25F and 42.56 Gy/16F groups and were all given tumor bed boosts. The two groups did not significantly differ in patient self-evaluations or clinicians' evaluations of the cosmetic outcomes. Tanguturi *et al.* (20) compared the above two trials (17,18) and found that HF-WBI had the same tumor control effect as that of CF-WBI, and HF-WBI was cheaper with fewer adverse reactions. HF-WBI should be strongly recommended for most EBC patients. Valle *et al.* (11) conducted a meta-analysis that further confirmed that HFRT did not worsen the late cosmetic effect compared with that of conventional fractionated radiotherapy (RR 0.95; 95% CI, 0.81–1.12), and HFRT may reduce the risk of acute radiation toxicity (RR 0.36; 95% CI, 0.21–0.62).

Considering the existing large randomized trial results

and guidelines and the convenience, effectiveness and safety of patients, priority should be given to HFRT. The 2018 National Comprehensive Cancer Network (NCCN) guidelines recommend that all breast tissue should receive 45 Gy/25F–50.4 Gy/28F or 40 Gy/15F–42.5 Gy/16F. For high-risk patients, such as those aged < 50 years with a high disease stage and positive lesion margins, a tumor bed boost at 10 Gy/4F–16 Gy/8F is recommended to reduce the risk of local recurrence. However, some tumor radiologists have questioned whether a single larger dose of radiation will increase the adverse effects of patients who have received chemotherapy or have a larger breast and whether it will increase the late toxicity of younger patients. Shaikh *et al.* (14) analyzed patients aged < 50 years who underwent HFRT and found that most patients had satisfactory cosmetic results. In a multicenter study, Shaitelman *et al.* (21) treated 287 patients with stage 0–II breast cancer. Patients were randomly divided into the HF-WBI group who received 42.56 Gy/16F + a 10–12.5 Gy/4–5F tumor bed boost and the CF-WBI group who received 50 Gy/25F + a 10–14 Gy/5–7F tumor bed boost. After a 4.1-year median follow-up, stratified analysis was performed according to chemotherapy, margin status, cosmetic effect and breast size. HF-WBI had a 5.4% lower incidence of adverse cosmetic outcomes compared with that of CF-WBI (8.2% *vs.* 13.6%, respectively, non-inferiority $P = 0.002$). Tumor bed boost, chemotherapy and large breasts do not seem to be an absolute contraindication for HF-WBI. HF-WBI can ensure effective treatment, provide adequate cosmetic and psychological support, and shorten the radiotherapy time to gain time for subsequent comprehensive treatment. However, the optimal HF-WBI fractionation dose, the concurrent/concomitant tumor bed boost, whether the concomitant increase in treatment time reduces the advantage of the hypofractionated short-course treatment, and whether HF-WBI can prioritize the concurrent boost remain uncertain. In addition, verifying advanced adverse reactions requires sufficient time for long-term follow-up.

Ductal carcinoma in situ (DCIS) HFRT

In recent years, HFRT has become increasingly widely used in low-risk groups. With increases in EBC screening, the detection rate of DCIS has improved greatly. Similarly, WBI after DCIS with BCS can reduce the risk of DCIS recurrence by approximately 55% (22). DCIS after BCS has fewer new breast events (absolute reduction of 12.6%) compared with those of patients who did not undergo

radiotherapy (23). Research has shown that HFRT at 50 Gy/25F seems to be equally effective in DCIS patients (24,25). In a study by Lalani *et al.* (24), the conventional fractionation group (n=971) received 50.0 Gy/25F, of which, 143 cases received a tumor bed boost, while in the hypofractionated group (n=638) received 40–44 Gy/16F, 346 cases received a tumor bed boost. After a median 9.2-year follow-up, the local recurrence-free survival rate of DCIS patients who underwent BCS was similar to that of those who underwent conventional fractionated radiotherapy (87% vs. 86%, respectively, P=0.03). DCIS after BCS in patients undergoing HFRT should not have an increased risk of local recurrence compared with that of patients undergoing conventional fractionated radiotherapy. However, the previous high-quality, large-sample study comprised a small proportion of DCIS patients, and no consensus exists regarding whether a tumor bed boost is needed after DCIS. Nilsson *et al.* (25) conducted a meta-analysis that found no difference in the risk of local recurrence between patients with DCIS after BCS [odds ratio (OR) 0.91; 95% CI, 0.77–1.08; P=0.28]. In patients with positive margins, the risk of local recurrence was reduced (OR 0.56; 95% CI, 0.36–0.87; P=0.01), and local recurrence rates did not differ between HF-WBI and CF-WBI (OR 0.78; 95% CI, 0.58–1.03; P=0.08). Thus, for DCIS patients after BCS, HFRT appears to be a safe adjuvant method. Ordinary DCIS patients received no benefit from the tumor bed boost, and the risk of local recurrence can be reduced in patients with positive margins. Vrieling *et al.* (26) showed that in young patients with invasive breast cancer and DCIS, a tumor bed boost can reduce the incidence of ipsilateral breast tumor recurrence (IBTR) from 20% to 15% [hazard ratio (HR) 0.37; 95% CI, 0.22–0.62; P<0.001]. Moran *et al.* (27) included 4,131 patients diagnosed with DCIS (no microinvasion) after BCS + WBI and divided them into the tumor bed boost (n=2,661) and no tumor bed boost (n=1,470) groups. The median follow-up was 9 years, and the median tumor bed boost was increased by 14 Gy. The results showed that patients with positive margins, oestrogen receptor (ER) body status, and acne-like necrosis were more likely to receive tumor bed boosts. Multivariate analysis showed that regardless of age or tamoxifen use, tumor bed boosts can significantly reduce IBTR (HR 0.68; 95% CI, 0.50–0.91; P=0.01), indicating that the tumor bed boost and the amount of the boost should be considered for patients with DCIS and a life expectancy of >10–15 years to reduce the risk of IBTR. The international mainstream opinion holds that for patients

with DCIS who have high-risk factors, such as an age of <40 years, high-grade nuclear margins, positive margins, or negative margins ≤ 2 mm, tumor bed boosts can reduce the risk of recurrence in the breast. In these cases, the amount of the tumor bed boost should be determined according to the risk and willingness of the patient to relapse.

HFRT for regional lymph nodes

Regional lymph node irradiation can further reduce local and distant recurrence and improve progression-free survival. However, the optimal dose of regional lymph node radiotherapy remains unknown. Some randomized studies have shown that HFRT is also effective and safe for treating regional lymph nodes (7,28,29). Haviland *et al.* (7), in the START A and START B trials, 14.2% and 7.3% of patients, respectively, received regional lymph node irradiation. The arm or shoulder symptoms evaluated by the patient and clinician at 10 years did not significantly differ between the HF-WBI and CF-WBI groups, and the appropriate doses of hypofractionated lymph node radiotherapy were safely obtained. Khan *et al.* (28) studied 69 women who underwent stage II–IIIa mastectomies. The radiotherapy target area included the chest wall and drainage-area lymph nodes. The median follow-up period was 32 months; the 3-year local recurrence-free survival rate was estimated at 89.2% (95% CI, 0.748–0.956), and the 3-year distant recurrence-free survival rate was estimated at 90.3% (95% CI, 0.797–0.956). Twenty-nine cases of grade 2 toxicity were reported, which mainly included grade 2 dermal toxicity (24%). No grade 3 toxicity was found. Thus, regional lymph node HFRT exhibits low toxicity and high local control. Wang *et al.* (29) enrolled 820 patients with high-risk breast cancer in a large randomized controlled trial and divided them into the conventional radiotherapy (CRT) group (50 Gy/25 F; 5 weeks; n=414) and HFRT group (43.5 Gy/15F; 3 weeks; n=406). The irradiation range was on the chest wall and the supraclavicular and axillary group III lymphatic drainage areas. After a 58.5-month median follow-up, the 5-year local recurrence rate was non-inferior to in the HFRT group than in the CRT group (8.3% vs. 8.1%, respectively; P<0.0001). The 5-year overall survival (84% vs. 86%) and 5-year disease-free survival (74% vs. 70%) rates not significantly differ between the HFRT and CRT groups. In terms of safety, fewer patients had grade 3 acute dermal toxicity in the HFRT group than in the CRT group (3% vs. 8%, P<0.0001), and no significant differences were found in the incidences of other acute or late toxic events, including

symptomatic radiation pneumonitis, lymphedema, ischemic heart disease, and shoulder dysfunction. No brachial plexus injury was seen in either group. Thus, HFRT is safe and effective for lymph node areas. Scholars have also mentioned that HFRT is soon expected to become the standard treatment program worldwide.

Partial-breast irradiation after BCS

To further shorten the treatment time and improve cosmetic effects, researchers in Europe and the Americas are conducting APBI research. APBI is based on many studies that have shown that most breast cancer recurrences after breast-conserving treatment are located in and around the tumor bed area, and the recurrence rate outside the tumor bed is extremely small. WBI does not appear to prevent new primary cancer development. Some low-risk patients who underwent BCS may not need WBI. The APBI irradiation range is the breast tumor bed, which effectively reduces the dose to surrounding organs such as the ipsilateral breast, skin, heart and lung. APBI also further shortens the treatment time, reduces the costs associated with radiation therapy, and brings convenience to patients. APBI can be achieved by brachytherapy or external irradiation techniques. Multiple randomized trials (30–34) show that APBI is a safe, effective, short-course adjuvant radiotherapy model.

In the IMPORT LOW trial, Coles *et al.* (30) randomized patients aged ≥ 50 years (pT1–2NO–1) into the WBI group (40 Gy/15F; n=674), the reduced-dose radiotherapy group (36 Gy/15F; n=673), and the local radiotherapy group containing the tumor bed (40 Gy/15F localized; n=669). In this study, the cumulative 5-year local recurrence rates in the WBI group, the reduced-radiation group, and the local radiotherapy group were estimated at 1.1%, 0.2%, and 0.5%, respectively. Compared with the WBI group, the absolute differences in local recurrence between the reduced-dose radiotherapy group and the local radiotherapy group were -0.73% and -0.38% , respectively, and the adverse reactions were significantly reduced, including changes in breast appearance (Plocal radiotherapy =0.007) and breast stiffness (Preduction radiotherapy =0.002; Plocal radiotherapy <0.0001). In terms of efficacy, reduced-dose radiotherapy and local radiotherapy were not inferior to WBI. Bhattacharya *et al.* (31) analyzed the IMPORT LOW trial and showed that the reduced radiotherapy (RR 0.83; 95% CI, 0.76–0.90; P<0.001) and local radiotherapy (RR 0.77; 95% CI, 0.71–0.84; P<0.001) groups had lower

adverse reactions than did the WBI group. In the GEC-ESTRO phase III clinical trial, Strnad *et al.* (32) divided patients aged ≥ 40 years with clinical stage 0–IIA breast cancer and BCS (cut margin ≥ 2 mm) into the APBI and WBI groups, of which, the APBI group (n=633) underwent multicatheter brachytherapy, and the WBI group (n=551) received 50 Gy WBI + tumor bed boost at 10 Gy. The main end-point was local recurrence rate. The results indicate that the local recurrence rate of APBI group and WBI group for 5 years has no significant differences between (1.44% vs. 0.92%), disease-free survival (95.03% vs. 94.45%), and overall survival (97.27% vs. 95.55%). Polgár *et al.* (33) reported secondary adverse end effects and cosmetic effects in the GEC-ESTRO phase III clinical trial. The results showed that the 5-year toxicities and side effects were similar between the APBI and WBI groups, and grade 2–3 late-stage skin side effects were significantly reduced in the APBI group (6.9% vs. 10.7%, P=0.020). At the 5-year follow-up, the WBI group was similar to the APBI group in terms of patient-assessed cosmetic outcomes (91% vs. 92%, P=0.62). The satisfaction rates for both groups, as evaluated by a physician, were similar (90% vs. 93%, P=0.12). For some patients with EBC, adjuvant APBI after BCS was as effective as the adjuvant WBI, achieved similar cosmetic results, and significantly reduced late-stage adverse effects to the skin. Schäfer *et al.* (34) reported the 5-year quality of life (QOL) in the GEC-ESTRO phase III clinical trial, which showed QOL scores of 65.5 ± 20.6 points in the APBI group and 64.6 ± 19.6 points in the WBI group before radiotherapy. These scores did not significantly differ (P=0.37). At 5 years, the QOL scores did not significantly differ between the APBI group at 66.2 ± 22.2 points and the WBI group at 66.0 ± 21.8 points (P=0.94). Compared with WBI, APBI does not reduce life quality.

The ASTRO Consensus Statement proposes that patients who are eligible for APBI are those aged ≥ 50 years, with a tumor diameter ≤ 2 cm, negative surgical margins ≥ 2 mm, lymph node (–), ER+, no lymphatic-vascular gap infiltration, and single-center lesions. DCIS should meet low- and medium-grade, the tumor diameter of ≤ 2.5 cm, and the surgical margin negative ≥ 3 mm simultaneously (35). The ESMO consensus also recommends that APBI is an acceptable treatment option for patients after BCS with a lower risk of local recurrence (16). However, its optimal dose-splitting scheme remains under study. Given the lack of large-scale clinical trials and limited long-term follow-up, its cosmetic effects remain controversial. In addition, because delayed radiotherapy may increase local recurrence

rates, the rational arrangement of sequential timing of radiotherapy and chemotherapy is controversial. Shortening the course of radiotherapy can enable timely intervention with other adjuvant treatments for breast cancer, which may solve the contradiction between the order and time of postoperative adjuvant chemotherapy and radiotherapy. Furthermore, safe and effective application of APBI suggests whether it can be treated with shorter course or fewer divisions in order to provide greater convenience and cost savings.

Application

Although the safety and effectiveness of HF-WBI has been verified and approved in guidelines, its application has increased but has not been fully utilized. In an analysis of 14 commercial health care plans in the United States regarding the use of HFRT in patients with early BCS increases, only 34.5% and 21.2% of women who hypofractionation-endorsed or hypofractionation-permitted received HFRT. Although HFRT reduces the medical costs associated with radiation therapy, its application is insufficient (36). A National Cancer Database (NCDB) analysis from 2004–2013 found that using HF-WBI in chemotherapy-treated breast cancer patients increased 4-fold, from 4.6% in 2004 to 18.2% in 2013 (37). According to the analysis, 72.5% and 50.4% of the IMPORT LOW and ASTRO guidelines were consistent with HF-WBI use, and many node-negative breast cancer patients who underwent BCS were eligible for HF-WBI (38). The US SEER database analyzed 108,484 patients with EBC and found that 80.1% and 75.0% of patients met the HF-WBI criteria according to the ASTRO guidelines and the IMPORT LOW criteria; thus, many patients with EBC who underwent BCS are eligible for HF-WBI (39).

Boero *et al.* (40) analyzed 22,233 patients with breast cancer who underwent BCS and found that the personal preference of tumor radiologists more strongly affected the use of HF-WBI than did the geographical region, clinical factors, or patient factors. Niska *et al.* (41) showed that using short-course radiotherapy in EBC can significantly reduce medical costs. For example, WBI uses 15 intensity-modulated radiotherapy sessions compared with 25 sessions, reducing the direct medical cost estimate by \$5,645.12. Currently, the proportion of HF-WBI used in clinical practice is not high, likely because the guidelines do not explicitly recommend HF-WBI for all patient populations

or because of concerns about its adverse reactions and individual tumor radiologists' preferences.

Accelerated cost-effectiveness of radiotherapy

In 2019, the United States was estimated to have had 1,762,450 new cancer cases. Of these, 62,930 new cases are estimated to be women with primary breast cancer (1); thus, annual breast cancer-assisted radiotherapy accounts for a large proportion of cancer treatment costs. Therefore, countries with limited resources must provide treatments with the same or better tumor control as that of standard treatments in less time and with low toxicity and costs. Deshmukh *et al.* (42) analyzed the cost-effectiveness of CF-WBI, intraoperative radiotherapy (IORT) and HF-WBI in patients with breast cancer after BCS. The 5-year follow-up showed that HF-WBI may be more cost-effective than IORT. If these negative effects after radiotherapy persist, the cost-benefit ratio (ICER) of the HF-WBI is \$17,024/quality-adjusted life years (QALYs), and the cost-benefit ratio will be 80% compared with that of IORT. If the negative utility is interrupted, the ICER value will be lower (\$11,461/QALY), and the cost-benefit ratio will be 83%. Compared with that of CF-WBI, HF-WBI will have higher QALYs and lower costs in any hypothetical situation. Thus, for women with EBC who need adjuvant radiotherapy, HF-WBI is the most cost-effective option. A subgroup analysis by Smith *et al.* (43) of 105,211 early-stage breast cancer patients (44,344 MarketScan, 60,867 SEER-Medicare) found that HF-WBI had similar complication rates as those of conventional WBI (MarketScan: RR = 0.99; 95% CI, 0.91–1.07; SEER-Medicare: RR = 1.01; 95% CI, 0.96–1.07), and the HF-WBI saved \$2,467 and \$4,462 per patient in MarketScan and SEER-Medicare respectively compared to traditional WBI. HFRT after BCS has good tumor control and cosmetic effects and is cost-effective. Shah *et al.* (44) conducted a cost-benefit analysis comparing APBI to HF-WBI + tumor bed boost and HF-WBI with no tumor bed boost. The direct cost savings were \$1,585 and \$700, and the indirect cost savings were \$2,951 and \$1,371. The QALY of APBI is 0.2300, and that of HF-WBI is 0.2289. Thus, APBI has better clinical outcomes and can reduce costs compared with HF-WBI. Short-course radiotherapy reduces costs and the stress of radiotherapeutic equipment and improves patient turnover, which can provide more treatment opportunities for patients, which is necessary for countries with limited radiotherapeutic resources.

Conclusions

Several international clinical trials have shown that HF-WBI is a safer treatment than CF-WBI, with similar survival and local control effects and tolerable adverse reactions. Among the appropriately selected populations, HF-WBI is also suitable for DCIS and is a reasonable method for treating regional lymph nodes. HF-WBI-accelerated radiotherapy shortens the radiotherapy duration, reduces costs, reduces the psychological and economic burdens to patients, and ensures the quality of life of patients. HF-WBI will likely become the main treatment for postoperative adjuvant radiotherapy for breast cancer.

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Footnote

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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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