Alternatives to Standard Fractionation Radiation Therapy After Lumpectomy

Hypofractionated Whole-Breast Irradiation and Accelerated Partial-Breast Irradiation

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KEYWORDS

• Breast cancer • Breast-conserving therapy • Lumpectomy • Standard fractionation • Hypofractionation • Accelerated partial-breast irradiation

KEY POINTS

- Adjuvant whole-breast irradiation after lumpectomy has been an established standard of care to optimize local tumor control for decades.
- Standard-fractionation whole-breast irradiation delivered over 5 to 7 weeks can achieve durable tumor control with low toxicity and favorable cosmesis but can be inconvenient and cost ineffective.
- Hypofractionated whole-breast irradiation can be completed in 3 to 4 weeks and is the preferred standard of care in appropriately selected patients.
- Accelerated partial breast irradiation can be delivered using even shorter treatment regimens, and early results suggest it is an effective alternative to WBI in select patients.
- Results from ongoing hypofractionated whole-breast irradiation and accelerated partial breast irradiation trials will help establish their roles in the adjuvant management of early stage breast cancer.

INTRODUCTION

Breast-conservation therapy, or breast-conserving surgery (BCS) followed by adjuvant radiation therapy (RT), was established as an acceptable alternative to mastectomy after multiple randomized trials conducted in the 1970s and 1980s demonstrated equivalent high survival rates with both approaches.[1,2] In 2005, the

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Early Breast Cancer Trialists' Collaborative Group meta-analysis further established breast-conservation therapy as the standard of care for early-stage breast cancer. The most commonly used radiation regimen in these randomized trials was 50 Gy in 25 fractions to the whole breast with or without a boost, now referred to as a *standard fractionation whole-breast irradiation* (SF-WBI).[3]

The radiobiological rationale in support of SF-WBI is that smaller doses of radiation per fraction can spare normal tissues, such as the breast, muscle, ribs, and lung, without compromising tumor control. Some of the challenges of SF-WBI, however, include the cost and inconvenience of 5 to 7 weeks of daily radiation treatment. As a result, there has been growing interest in establishing alternate methods of delivering adjuvant RT using shorter and more convenient regimens. This article reviews hypofractionated WBI (HF-WBI) and accelerated partial breast irradiation (APBI) as accepted alternate approaches to SF-WBI in appropriately selected patients with early-stage breast cancer.

HYPOFRACTIONATED WHOLE-BREAST IRRADIATION

HF-WBI refers to the delivery of adjuvant whole-breast RT in a shortened 3- to 4-week course of treatment. The evidence in support of HF-WBI comes from a series of large randomized trials showing equivalence in efficacy, toxicity, and long-term cosmesis compared with SF-WBI. Key features and results of each trial are summarized in **Tables 1** and **2**.

EFFICACY OF HYPOFRACTIONATED WHOLE-BREAST IRRADIATION

One of the earlier HF-WBI trials was initiated in 1986 at the Royal Marsden Hospital and Gloucester Oncology Center (RMH/GOC) in the United Kingdom. This was a pilot trial that included 1410 patients younger than 75 years of age with T1-3, N0-1, M0 breast cancer who underwent BCS with complete macroscopic resection of invasive

Table 1
Key features of randomized breast hypofractionation trials

Variable	RMH/GOC	START A	START B	Canadian
Patients enrolled	1410	2236	2215	1234
Study years	1986–1998	1998–2002	1999–2001	1993–1996
Median follow-up (y)	9.7	9.3	9.9	12.0
Stage	T1-3, N0-1, M0	T1-3a, N0-1, M0	T1-3a, N0-1, M0	T1-2, N0, M0
Surgery				
Lumpectomy, N (%)	1410 (100)	1900 (85)	2038 (92)	1234 (100)
Mastectomy, N (%)	0	336 (15)	117(8)	0
Treatment arms (Gy/fractions)	50/25 (5 wk) 42.9/13 (5 wk) 39/13 (5 wk)	50/25 (5 wk) 41.6/13 (5 wk) 39/13 (5 wk)	50/25 (5 wk) 40/15 (3 wk)	50/25 (5 wk) 42.5/16 (3.2 wk)
Boost				
N (%)	1051 (75)	1159 (61)	875 (43)	0
Dose (Gy/fractions)	14/7	10/5	10/5	
Regional nodal irradiation, N (%)	290 (21)	318 (14)	161 (7)	0
Chemotherapy, N (%)	196 (14)	793 (35)	491 (22)	135 (11)

Table 2
Key results of randomized breast hypofractionation trials

	RMH/GOC				START A				START B			Canadian		
10-y Endpoints	**50 Gy (%)**	**42.9 Gy (%)**	**39 Gy (%)**	***P* Value**	**50 Gy (%)**	**41.6 Gy (%)**	**39 Gy (%)**	***P* Value**	**50 Gy (%)**	**40 Gy (%)**	***P* Value**	**50 Gy (%)**	**42.5 Gy (%)**	***P* Value**
Local recurrence	12.1	9.6	14.8	NS[a]	6.7	5.6	8.1	NS	5.2	3.8	NS	6.7	6.2	NS
Distant metastasis	—	—	—	—	14.7	16.8	18.0	NS	16.0	12.3	.014	—	—	—
All-cause mortality	—	—	—	—	19.8	18.4	20.3	NS	19.2	15.9	.042	15.6	15.4	NS

Abbreviation: NS, not significant.
[a] Not significant when each experimental arm was compared with the control arm.

carcinoma. Patients were randomly assigned to 3 radiation dose schedules all delivered over 5 weeks. The control arm consisted of 50 Gy in 25 daily fractions. The 2 experimental HF-WBI arms delivered 42.9 Gy in 13 fractions (3.3 Gy per fraction) and 39 Gy in 13 fractions (3 Gy per fraction), with 2 to 3 fractions delivered per week. A subrandomization to a 14-Gy electron boost in 7 fractions was also performed. The risk of ipsilateral tumor recurrence at 10 years was 12.1% in the 50-Gy arm, 9.6% in the 42.9-Gy arm, and 14.8% in the 39-Gy arm. There was no significant difference in local recurrence when comparing each HF-WBI arm with the SF-WBI arm.[4]

The UK Standardization of Breast Radiotherapy Trial A (START A) included 2236 women with operable T1-3a, N0-1, M0 invasive breast cancer who underwent surgical resection with clear $\geq$1-mm margins. Although both BCS and mastectomy were allowed, only 15% of enrolled patients underwent mastectomy. Patients were randomly assigned to receive 50 Gy in 25 fractions (control arm), or 41.6 Gy in 13 fractions, or 39 Gy in 13 fractions (experimental arms). All treatments were delivered over 5 weeks, similar to the RMH/GOC study. Boost (10 Gy/5 fractions) was delivered at the discretion of the treating physician in about 61% of patients. About 14% of patients received regional nodal irradiation (supraclavicular nodes $\pm$ axillary nodes), and about 35% received adjuvant chemotherapy before radiation. Rates of local relapse at 10 years were 6.7% in the 50-Gy arm, 5.6% in the 41.6-Gy arm, and 8.1% in the 39-Gy arm (*P* value, not significant). Both disease-free survival (DFS) and overall survival (OS) were similar among all arms.[5,6]

The START B trial had similar inclusion criteria and randomized 2215 patients to 50 Gy in 25 fractions or 40 Gy in 15 fractions. Unlike in the RMH/GOC and START A trials, patients on the HF-WBI arm completed radiation treatment in only 3 weeks. A total of 8% of patients underwent mastectomy, 43% received a boost, 7% received regional nodal irradiation, and 22% received adjuvant chemotherapy. The 10-year local relapse rate was 5.2% in the 50-Gy arm and 3.8% in the 40-Gy arm (*P* value, not significant). Surprisingly, distant relapse, DFS, and OS were all significantly improved in the 40-Gy arm. It is unclear what drove the improvement in DFS and OS, as the difference in local tumor control was likely too small to translate into a survival benefit.[6,7]

The Canadian trial randomly assigned 1234 patients with T1-2, N0, M0 invasive breast cancer to SF-WBI with 50 Gy in 25 fractions delivered over 5 weeks or HF-WBI with 42.5 Gy in 16 fractions delivered in just more than 3 weeks. Unlike previous trials, patients who underwent mastectomy and those with node-positive disease were not eligible, and lumpectomy boost and nodal irradiation were not allowed. Most patients (75%) were older than 50 years of age, and only 11% received adjuvant chemotherapy. At 10 years, local recurrence rates were 6.7% in the SF-WBI arm and 6.2% in the HF-WBI arm (*P* value, not significant). Ten-year OS rates were also nearly identical (84.4% and 84.6%, respectively). In an unplanned subgroup analysis, both treatment regimens were equally effective regardless of patient age, tumor size, estrogen receptor status, or receipt of systemic therapy. In patients with high-grade disease, however, 10-year local recurrence was higher in the HF-WBI arm (15.6% vs 4.7%; $P = .01$).[8]

Long-term Toxicity and Cosmesis of Hypofractionated Whole-Breast Irradiation

In the RMH/GOC trial, long-term rates of fair or poor cosmesis, breast shrinkage, breast distortion, breast edema, and induration were lowest in the 39-Gy arm, although a direct comparison with the 50-Gy arm was not made.[9]

Long-term physician-assessed tissue effects in the START A trial showed similar rates of breast shrinkage, shoulder stiffness, and arm edema among all treatment arms at 10 years. The 39-Gy arm had significantly lower rates of breast edema and telangiectasias compared with the 50-Gy arm. There were no significant differences between the 41.6-Gy and 50-Gy arms. Similar results were seen in START B, with lower rates of breast edema, telangiectasia, and breast shrinkage in the 40-Gy arm. Rates of other late adverse effects including symptomatic rib fracture, symptomatic lung fibrosis, ischemic heart disease, and brachial plexopathy were low (<3%) among all treatment arms in the START A and START B trials.[6]

In the Canadian trial, rates of skin and subcutaneous tissue toxicity at 10 years were similar in the 50-Gy and 42.5-Gy arms. An excellent or good cosmetic outcome was achieved in 69.8% of patients in the HF-WBI arm compared with 71.3% of patients in the SF-WBI arm.

Consensus statement on hypofractionated whole-breast irradiation

In 2011, the American Society for Radiation Oncology (ASTRO) consensus guidelines endorsed HF-WBI as an equally effective regimen compared with SF-WBI for select patients with early-stage breast cancer. Patients were candidates for HF-WBI if they were age 50 years or older at the time of diagnosis, had pathologic T1-2, N0 disease treated with BCS, and did not receive chemotherapy. During treatment planning, it was recommended that the dose within the breast along the central axis should not be lower than 93% or higher than 107% of the prescription dose. For patients who did not meet all criteria, there was no consensus recommendation for or against HF-WBI.[10] ASTRO is currently developing an updated consensus statement on WBI fractionation that is anticipated to be released later this year.

Clinical considerations for hypofractionated whole-breast irradiation

Hypofractionated whole-breast irradiation and boost Although a considerable number of patients enrolled on the RMH/GOC and START A and B trials received a boost, as summarized in **Table 1**, the ASTRO guidelines did not provide a consensus opinion regarding the integration of a breast boost into a HF-WBI regimen. Approximately half of the patients enrolled on the RMH/GOC trial underwent a second randomization for a boost versus no boost, and the remaining half received an elective boost of 14 Gy in 7 fractions. A 10 Gy/5 fraction boost was planned in 61% of patients in the START A trial and 43% of patients in the START B trial. In 2013, post-hoc subgroup analyses compared the combined hypofractionated regimens with the control arms in the RMH/GOC, START A, and START B trials. Tumor control and normal tissue outcomes were similar irrespective of tumor bed boost, suggesting that a breast boost can safely be incorporated into a HF-WBI regimen. These data were published after the 2011 ASTRO guidelines.[6,10]

Hypofractionated whole-breast irradiation and regional nodal irradiation Current guidelines do not endorse HF-WBI in node-positive patients who require regional nodal irradiation.[10] A small proportion of patients enrolled on the RMH/GOC (21%), START A (14%), and START B (7%) trials did receive hypofractionated regional nodal irradiation (see **Table 1**). There was no evidence of increased late adverse effects with regard to shoulder stiffness, arm edema, brachial plexopathy, and lung fibrosis in these trials. However, the most clinically relevant HF-WBI schedule was used in the START B trial in which treatment was completed in 3 weeks, and only 7% of patients received regional nodal irradiation in this analysis.[6]

A recent prospective single arm phase II postmastectomy hypofractionation trial treating the chest wall and regional lymphatics using a novel 3-week fractionation

scheme showed acceptable toxicity and outcomes.[11] To further evaluate the safety and efficacy of hypofractionation to the regional nodes, the Alliance Cooperative Group has launched a phase III trial randomly assigning node-positive patients who have undergone modified radical mastectomy with reconstruction to standard fractionation versus hypofractionation (42.5 Gy in 16 daily fractions) to the chest wall/breast and regional lymphatics.[12]

Hypofractionated whole-breast irradiation and chemotherapy The proportion of patients who received chemotherapy in the RMH/GOC, START A, START B, and Canadian trials ranged from 11% to 35% (see **Table 1**), with an even smaller number of patients in the START A and START B trials receiving anthracycline-containing and taxane-containing regimens. Long-term combined results from the RMH/GOC, START A, and START B trials again showed no change in tumor control and normal tissue outcomes with chemotherapy receipt. Although the 2011 ASTRO guidelines did not reach consensus on the use of HF-WBI after chemotherapy, most task force members reported they commonly used HF-WBI after systemic chemotherapy. Additional long-term data on chemotherapy were not available at the time of the 2011 ASTRO consensus.[6,10] The use of HF-WBI after chemotherapy will likely be revisited in the updated consensus guidelines currently under development.

Hypofractionated whole-breast irradiation and ductal carcinoma in-situ Multiple large randomized trials have found the benefits of adjuvant SF-WBI after BCS in reducing the risk of local recurrence for ductal carcinoma in-situ (DCIS).[13–16] The available data in support of HF-WBI for adjuvant management of DCIS comes largely from single and multi-institutional retrospective series.[17–20] A meta-analysis of 2534 patients from 4 studies comparing HF-WBI with SF-WBI for DCIS showed no difference in local recurrence rates with HF-WBI.[21] Although the randomized Canadian trial did include patients with a DCIS component, patients with only DCIS were not studied. In clinical practice, the use of HF-WBI for DCIS is extrapolated from randomized data on invasive carcinoma.

Utilization of hypofractionated whole-breast irradiation

HF-WBI has the potential to reduce treatment cost and increase patient convenience while maintaining tumor control and long-term normal tissue toxicity. In 2013, the American Society of Radiation Oncology encouraged the Choosing Wisely initiative, which is a national campaign in the United States aimed at reducing low-value health care, to discuss the use of HF-WBI in appropriately selected patients with early-stage breast cancer.[22,23]

National cancer registry data show an overall increase in the utilization of HF-WBI. A National Cancer Data Base analysis showed an increase in HF-WBI utilization from 5.4% in 2004 to 22.8% in 2011.[24] Similarly, a Surveillance, Epidemiology, and End Results (SEER) analysis found that the use of HF-WBI increased from 3.8% in 2006 to 13.6% in 2010.[25] Another analysis using administrative claims data showed an increase in HF-WBI from 10.6% in 2008 to 34.5% in 2013 among patients for whom HF-WBI was endorsed by the 2011 ASTRO guidelines. Adjusted mean total health care expenditures 1 year after diagnosis were nearly $3000 lower for patients who received HF-WBI compared with SF-WBI ($28,747 vs $31,641), translating into a mean total health care expenditure savings of 9.1%.[26]

Although national utilization rates of HF-WBI have increased substantially over recent years, a significant proportion of patients with early-stage breast cancer continue to receive SF-WBI. The reluctance of clinicians to adopt HF-WBI as a standard of care may stem, in part, from several remaining questions regarding the safety

and efficacy of HF-WBI in certain clinical scenarios, as previously discussed. However, a utilization rate of only 34.5% in patients for whom HF-WBI was endorsed suggests additional factors, such as reimbursement rates, may also play a role.

Accelerated Partial Breast Irradiation

Accelerated partial breast irradiation (APBI) targets RT to the breast tissue surrounding the postlumpectomy surgical cavity, which is considered to be the region at highest risk for recurrence. In addition to treating a smaller target volume, APBI can be delivered using shorter treatment regimens compared with SF-WBI and HF-WBI. A variety of techniques can be used for the delivery of APBI, including multicatheter interstitial brachytherapy, balloon catheter brachytherapy, 3-dimensional conformal RT (3D-CRT), and intraoperative RT (IORT).

Multicatheter interstitial brachytherapy

Multicatheter interstitial brachytherapy was the earliest technique developed for treatment of the partial breast with the longest available follow-up data. The Radiation Therapy Oncology Group (RTOG) 95-17 trial was a multi-institutional prospective phase II study that enrolled patients with stage I or II unifocal breast cancer less than 3 cm in size after lumpectomy with negative margins. Axillary dissection was required with a minimum of 6 lymph nodes recovered. Patients with up to 3 positive lymph nodes without extracapsular extension were allowed. Patients with DCIS, invasive lobular carcinoma, or extensive intraductal component were excluded. Patients who received low-dose-rate (LDR) brachytherapy were treated to a dose of 45 Gy in 3.5 to 5 days, and those who received high-dose-rate (HDR) brachytherapy were treated to a dose of 34 Gy in 10 fractions delivered twice daily. Long-term results from 98 evaluable patients showed a 10-year ipsilateral breast recurrence (IBR) rate of 5.2%. Ten-year DFS and OS rates were 69.8% and 78.0%, respectively.[27]

A smaller phase I/II protocol included 48 patients with T1, N0, M0 breast cancer who received LDR after lumpectomy to doses of 50 Gy, 55 Gy, and 60 Gy. The treatment volume included the lumpectomy cavity with a 3-cm margin. The 12-year IBR rate from this study was 14.6%. Two-thirds of patients reported good or excellent cosmesis.[28] A third series included 45 patients with T1, N0-N1mi breast cancer treated with HDR brachytherapy to 30.3 Gy or 36.4 Gy delivered over 4 days. The 12-year rate of local recurrence was 9.3%. Good or excellent cosmesis was achieved in nearly 80% of patients.[29]

A larger multi-institutional phase III noninferiority trial randomly assigned 1184 patients with stage 0, I, and IIA breast cancer who underwent BCS to either SF-WBI or APBI. Patients randomly assigned to the APBI arm received HDR multicatheter brachytherapy to a dose of 32 Gy in 8 twice-daily fractions or 30.3 Gy in 7 twice daily fractions. The 5-year local recurrence rates were 0.92% in the SF-WBI arm and 1.44% in the APBI arm (*P* value, not significant), which was below the relevance margin of 3%. There was no significant difference in 5-year DFS or OS. Skin and subcutaneous tissue toxicity rates remained low in both arms. Long-term follow-up is needed to establish durable tumor control with APBI.[30]

Balloon catheter brachytherapy

The use of the MammoSite (Hologic, Bedford, MA) balloon applicator was approved by the US Food and Drug Administration in 2002. Compared with interstitial brachytherapy, balloon catheter brachytherapy allows for simplified catheter insertion. The American Society of Breast Surgeons MammoSite Registry Trial included 1449 patients treated at 97 participating institutions. Study inclusion criteria were age 45 years

or older, tumor size 2 cm or less, invasive ductal carcinoma or ductal carcinoma in situ histology, and negative surgical margins. Technical guidelines, such as balloon-to-skin distance of 7 mm or more and cavity size, were also provided. After lumpectomy, patients were treated to a dose of 34 Gy in 10 fractions delivered twice daily. The 7-year actuarial rate of IBR was 5.8%. For patients with long-term data on cosmesis, good or excellent cosmetic outcome was achieved in more than 90%.[31]

Three-dimensional conformal radiation therapy

The major advantage of 3D-CRT APBI is its accessibility at a wider range of centers, as treatment is not limited to facilities with brachytherapy capabilities. Several randomized studies compared WBI with 3D-CRT APBI. The Christie Hospital Breast Conservation Trial randomly assigned 708 patients to WBI (40 Gy in 15 fractions) or tumor bed–only irradiation using electrons (40–42.5 Gy in 8 fractions). At a median follow-up of 5.4 years, patients with infiltrating ductal carcinoma had an IBR rate of 15% with APBI compared with 11% with WBI. For patients with infiltrating lobular carcinoma, the increase in IBR with APBI was significantly larger (34% APBI vs 8% WBI).[32] A similar study randomly assigned patients to WBI (40 Gy in 15 fractions) or partial-breast irradiation (55 Gy in 20 fractions with electrons). Although statistical analysis was limited because of poor accrual, the rate of IBR was higher with partial-breast irradiation (12% vs 4%; *P* value, not significant).[33]

The Canadian Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) enrolled 2135 women age older than 40 years with node-negative invasive ductal carcinoma or DCIS measuring $\leq$3 cm. Patients were randomly assigned after BCS to WBI (either 42.5 Gy in 16 fractions or 50 Gy in 25 fractions with or without a boost) versus 3D-CRT APBI (38.5 Gy in 10 fractions delivered twice daily without a boost). The trial was closed to accrual in 2011, and final results are not yet available. However, an interim analysis found significantly inferior cosmetic outcomes in the APBI arm based on patient, nurse, and physician assessment. The rate of grade 3 toxicity was very low in both arms, but grade 1 and 2 toxicities were more common in the APBI arm.[34] In contrast, a long-term update of the RTOG 0319 trial, a smaller phase 1 and 2 trial evaluating 3D-CRT APBI, showed a 7-year IBR rate of 5.9% and a grade 3 adverse event rate of 7.7%. However, this study only evaluated 52 patients.[35]

Intraoperative radiation therapy

Intraoperative APBI (IO-APBI) is a newer technique that uses applicators to deliver low-energy photons immediately after lumpectomy. Although this treatment can be very convenient for patients and shows promising early results, long-term efficacy data are not yet available. An additional limitation to IO-APBI is the incomplete knowledge of tumor pathology at the time of surgery and treatment.

The TARGIT-A trial was a randomized, phase 3 noninferiority trial that included 3451 patients. Women were randomly assigned to conventional WBI (per each center's protocols) versus a single fraction of 20 Gy immediately after lumpectomy prescribed to the surface of the applicator. Postoperative WBI was permitted for predefined pathologic features at the discretion of the treating institution. The primary endpoint was local recurrence, and noninferiority of IO-APBI was defined as a less than 2.5% absolute difference. The 5-year local recurrence rate was 3.3% in the IO-APBI arm compared with 1.3% in the WBI arm, which met the noninferiority criteria. Toxicity was also similar between the 2 treatment arms.[36]

The ELIOT trial was an equivalence trial that randomly assigned 1305 patients to WBI (50 Gy in 25 fractions with a 10-Gy boost) versus IORT (21 Gy in 1 fraction). The 5-year IBR rate was 4.4% in the IORT group compared with 0.4% in the WBI

group. Although this finding met the equivalence criteria, the rate of IBR after IORT was significantly higher than that after WBI.[37]

Consensus statements on accelerated partial breast irradiation

ASTRO released a consensus statement regarding the use of APBI after lumpectomy in 2009. Patients classified as suitable for APBI included those who were older than 60 years, had T1, N0 tumors, had positive estrogen receptor (ER) status, had no lymphovascular space invasion (LVSI), had widely (>2 mm) negative margins, and had no multicentric disease. The cautionary group included any patients with one of the following criteria: age less than 60, T2 tumor, pure DCIS less than 3 cm, close margins (<2 mm), focal LVSI, multifocal or multicentric disease, invasive lobular carcinoma, or ER negativity. Unsuitable patients included those with tumors greater than 3 cm, positive margins, positive lymph nodes, no axillary surgery, extensive LVSI, multicentricity, DCIS greater than 3 cm, and those with a BRCA 1 or 2 mutation. The Task Force did not specify a preferred APBI technique.[38]

After additional data on the efficacy of APBI became available, ASTRO released a revised consensus statement in 2016, which is summarized in **Table 3**. The suitable group was modified to include patients age 50 years or older and patients with

Table 3
Summary of American Society for Radiation Oncology consensus statement

Variable	Suitable	Cautionary	Unsuitable
Age, y	≥50	40–49 if otherwise suitable ≥50 if at least one cautionary feature is present	<40 40–49 if cautionary criteria not met
Tumor size	≤2 cm	2.1–3.0 cm	>3 cm
N stage	pN0		pN1-3
Margins	≥2 mm	<2 mm	Positive
LVSI	None	Focal	Extensive
ER status	Positive	Negative	
Multicentricity	Clinically unifocal, microscopic multifocality allowed if total lesion size is ≤2 cm	Clinically unifocal, microscopic multifocality allowed if total lesion size is 2.1–3.0 cm	Clinically multifocal or microscopic multifocality with total lesion size >3.0 cm
Histology	Invasive ductal	Invasive lobular	
Pure DCIS	Allowed if screen-detected, low-intermediate grade, size ≤2.5 cm, negative margins ≥3 mm	≤3 cm and does not meet suitable criteria	
Nodal surgery	SLNB or ALND		None
Neoadjuvant therapy	No		Yes
BRCA1/2 mutation	No		Yes

Abbreviations: ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

low-risk DCIS (low-intermediate grade, size $\leq$2.5 cm, $\geq$3 mm margins, as per RTOG 9804). The cautionary group was modified to include patients age 40 to 49 years if all other criteria in the suitable category were met.

Future Directions

Both HF-WBI and APBI represent more convenient and potentially cost-effective treatment modalities compared with SF-WBI. Although long-term efficacy data for HF-WBI are available, there are some remaining questions regarding the optimal candidates for HF-WBI, as previously discussed. Additionally, there is interest in further shortening the treatment regimen to provide greater convenience and cost savings.

The UK FAST trial randomly assigned 915 women age 50 years or older with node-negative early breast cancer to SF-WBI with 50 Gy in 25 daily fractions versus HF-WBI with 28.5 Gy or 30 Gy in 5 once-weekly fractions. Preliminary results showed similar rates of adverse effects in the breast between the 28.5-Gy and 50-Gy regimens. Tumor control rates have not yet been evaluated.[39] The FAST-Forward trial is a phase III randomized trial comparing 40 Gy in 15 daily fractions to 26 Gy or 27 Gy in 5 daily fractions. The trial enrolled 4100 patients with a primary endpoint of ipsilateral breast tumor control. Results are pending.[40]

The fractionation schemes of 42.5 Gy in 16 daily fractions from the Canadian trial and 40 Gy in 15 daily fractions from the START B trial are the most appropriate HF-WBI schemes outside of a clinical trial and are the most commonly used regimens in current day practice. Other smaller prospective phase II trials have evaluated alternate schemes that deliver equivalent radiobiologic doses with promising results. One series evaluating a 3-week regimen consisting of 36.63 Gy in 11 fractions to the whole breast followed by a lumpectomy bed boost in 4 fractions of 3.33 Gy showed high local control rates, low toxicity, and favorable cosmetic outcomes on short-term follow-up.[41] Another series showed the feasibility of using accelerated whole-breast intensity modulated RT in the prone position to reduce normal tissue exposure and spare the heart and lung. A dose of 40.5 Gy in 15 daily fractions was delivered to the whole breast with a concomitant boost of 0.5 Gy to the lumpectomy cavity, for a total dose of 48 Gy to the tumor bed.[42]

Data on the use of HF-WBI for postmastectomy irradiation and regional nodal irradiation remains limited. A recent phase II study evaluating a 3-week regimen for treatment of the chest wall and regional lymphatics showed favorable results.[11] The safety and efficacy of hypofractionation to the regional nodes is also being studied in a recently launched phase III randomized trial.[12] Until these data mature, SF-WBI will likely remain the most commonly used regimen for patients requiring regional nodal irradiation. An ongoing Trans-Tasman Radiation Oncology Group trial is investigating the role of HF-WBI for DCIS.[43]

Although the available efficacy data on APBI is encouraging, it is largely limited by inadequate follow-up. Two large randomized trials were recently closed to accrual, and, once mature, their results should help to establish the long-term efficacy and toxicity of APBI. The RAPID trial, as previously discussed, enrolled 2135 women with node-negative invasive ductal carcinoma or DCIS to WBI versus 3D-CRT APBI. The National Surgical Adjuvant Breast and Bowel B-39/RTOG 0413 trial is a randomized phase III study comparing SF-WBI with APBI using multicatheter interstitial brachytherapy, balloon catheter brachytherapy, or 3D-CRT APBI. This trial completed enrollment in 2013 and includes 4311 patients with stage 0, I, or II breast cancer with primary tumor size $\leq$3 cm and no more than 3 positive lymph nodes. Patients age 18 and older with unifocal invasive adenocarcinoma or DCIS were eligible. Negative lumpectomy margins and axillary evaluation were required. Once available, results

from this trial and those from the recently closed RAPID trial may help address several questions regarding APBI, such as the appropriate patient age criteria, suitability for DCIS, and which technique provides the greatest long-term tumor control.[34,44]

SUMMARY

Adjuvant whole-breast irradiation after BCS has been an established standard of care to optimize local tumor control for decades. Although SF-WBI can achieve excellent durable tumor control with low toxicity and favorable cosmesis, a 5- to 7-week treatment regimen can be inconvenient for patients and may be an ineffective use of available resources.

HF-WBI presents an appealing alternate treatment regimen and may be considered the preferred standard of care in appropriately selected patients. The long-term data on APBI are more limited, but the available results suggest it is an effective alternative to WBI in certain subsets of patients.

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