Frontiers in Radiotherapy for Early-Stage Invasive Breast Cancer

Christine M. Fisher and Rachel Rabinovitch

All authors: University of Colorado Hospital, Aurora, CO.

Published online ahead of print at www.jco.org on August 11, 2014.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Rachel Rabinovitch, MD, University of Colorado Hospital, 1665 Aurora Court, Suite 1032, Aurora, CO 80045; e-mail: rachel.rabinovitch@ucdenver.edu.

© 2014 by American Society of Clinical Oncology

0732-183X/14/3226w-2894w/\$20.00

DOI: 10.1200/JCO.2014.55.1184

ABSTRACT

The development of breast-conserving treatment for early-stage breast cancer is one of the most important success stories in radiation oncology in the latter half of the twentieth century. Lumpectomy followed by radiotherapy provides an appealing alternative to mastectomy for many women. In recent years, there has been a shift in clinical investigational focus toward refinements in the methods of delivering adjuvant radiotherapy that provide shorter, more convenient schedules of external-beam radiotherapy and interstitial treatment. Expedited courses of whole-breast treatment have been demonstrated to be equivalent to traditional lengthier courses in terms of tumor control and cosmetic outcome and to provide an opportunity for cost efficiencies.

J Clin Oncol 32:2894-2901. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Sir Geoffrey Langdon Keynes, MD Cambridge, F.R.C.S. (1887-1982) was a lieutenant in the Royal Army Medical Corp in World War I, a Royal Air Force air vice-marshal in World War II, the first surgeon to successfully perform thymectomy for myasthenia gravis, the husband of Charles Darwin's granddaughter, the brother of one of the most influential economists of the twentieth century, the brother-in-law of the winner of the 1922 Nobel Prize in Medicine and Physiology, and a renowned literary scholar with a special interest in William Blake.^{1,2} Such an illustrious vita would warrant interest in the life and work of Keynes for many reasons, but the particular accomplishment of interest for this discussion is Sir Geoffrey's boldly disruptive, novel, and groundbreaking work in the organ-preserving management of breast cancer—an approach that continues to evolve today and remains one of the most important clinical indications for radiotherapy.

The title of Keynes' 1937 contribution to the *British Journal of Surgery*, "Conservative treatment of breast cancer,"³ is possibly the first use of this phrase. A 1928 publication in *The Lancet* first recorded the technical details of interstitial radium treatment for breast cancer, including a summary of the outcomes for the first 42 patients treated,⁴ and a later report offered a perspective on the creative sparks that prompted his departure from the routine approach of the day, the Halsted mastectomy. Keynes acknowledged the influence of his mentor, Professor George Gask, who first suggested the idea

of radium-based breast-conserving therapy, and the anatomic studies of his contemporary J.H. Gray as a guide to rationally selecting the areas of regional lymphatic drainage to cover.³

In the United States, pioneering efforts in the early 1970s led by Leonard Prosnitz, MD, at Yale and Samuel Hellman, MD, at the Joint Center for Radiation Therapy led to the first publications describing the successful combination of lumpectomy and external-beam radiotherapy to achieve excellent rates of disease control and cosmetic results.⁵⁻⁷ From there, the clinical investigations of this treatment paradigm expanded into large-scale randomized studies comparing this strategy against mastectomy, exemplified by the National Surgical Adjuvant Breast and Bowel Project B-06 (NSABP-B-06; A Protocol to Compare Segmental Mastectomy and Axillary Dissection With and Without Radiation of the Breast and Total Mastectomy and Axillary Dissection) study that established the safety and efficacy of this approach for properly selected patients.⁸⁻¹³

More recent investigations have focused on the continued refinement of this strategy by implementing state-of-the-art treatment delivery techniques that include external-beam radiotherapy-based approaches as well as modern forms of brachytherapy. The questions posed have addressed how efficiently whole-breast irradiation (WBI) can be delivered and how narrowly the radiation treatment can be focused. For the purposes of this review, these issues will be categorized into studies of hypofractionated WBI (HF-WBI), accelerated

	Week 1	Week 2	Week 3	Week 4	Week 5	Total dose	Fractionation
Standard fractionation						50 Gy	2 Gy × 25
RMH/GOC						39 Gy 42.9 Gy	3 Gy × 13 3.3 Gy × 13
START A						39 Gy 41.6	3 Gy × 13 3.2 Gy × 13
START B						40 Gy	2.67 Gy × 15
Canadian						42.5 Gy	2.66 Gy × 16
UK FAST						28.5 Gy 30 Gy	5.7 Gy × 5 6 Gy × 5
FAST-Forward						26 Gy 27 Gy	5.2 Gy × 5 5.4 Gy × 5

Fig 1. Summary of fractionation schedules tested in randomized trials. RMH/GOC, Royal Marsden Hospital/Gloucester Oncology Center; START A, Standardization of Breast Radiotherapy Trial A; START B, Standardization of Breast Radiotherapy Trial B; Canadian, Randomized Trial of Breast Irradiation Schedules After Lumpectomy for Women With Lymph Node–Negative Breast Cancer; UK FAST, United Kingdom FAST Trial (Radiation Therapy in Treating Women With Localized Breast Cancer); FAST-Forward, Randomized Clinical Trial Testing a One Week Course of Curative Whole Breast Radiotherapy Against a Standard Three Week Schedule in Terms of Local Cancer Control and Late Adverse Effects in Patients With Early Breast Cancer.

partial-breast irradiation (APBI), and intraoperative radiotherapy (IORT).

HF-WBI

The drive toward shorter treatment schedules in the management of breast cancer is one of many illustrations of an overarching momentum across the field of radiation oncology toward exploring the use of fewer treatments for a wide variety of cancers.¹⁴ In some cases, the intent is to intensify the radiotherapy to a dose that ablates gross disease,¹⁵ and in other cases, to offer greater efficiency and cost-effectiveness.

In the six randomized trials that established the equivalence in efficacy of lumpectomy and whole-breast radiotherapy (WBRT) over 5 weeks to mastectomy,^{8–13} the radiotherapy was delivered daily (Monday–Friday) in doses of 2 Gy each (standard fraction WBI [SF-WBI]). The traditional dogma in support of SF-WBI for breast cancer is that radiation damage to normal tissue (breast, muscle, ribs, and lung) is greater with larger doses per fraction, without additional tumor control. As a result, SF-WBI in the treatment of an intact breast after lumpectomy has been the norm for several decades.

Some of the challenges of breast radiotherapy are the time and cost involved with daily treatment courses spanning 5 to 7 weeks; for this reason, many patients who are candidates for breast conservation opt for mastectomy instead. With these concerns and new radiobiology considerations in mind, randomized trials comparing SF-WBI to treatment schedules that use larger doses per treatment and fewer total treatments (such as HF-WBI) have been performed. The smaller number of HF-WBI treatments in these trials are either spread out over 5 weeks or delivered daily and conclude in shorter periods of time.^{16–18} All published trials have used treatment schedules involving 13 to 16 treatments to the whole breast over 3 to 5 weeks. With mature follow-up of 10 years in all trials, which together treated more than

6,500 patients, these studies demonstrate that hypofractionation (HF) yields equivalent or improved outcomes in all essential end point parameters: efficacy (both local and distant disease control), toxicity, cosmesis, and cost-effectiveness. HF-WBI also results in greater patient convenience and resource efficiency.

Trial Designs and Tumor Outcomes

The mature published randomized trials on which our current understanding of accelerated fractionation in WBRT is based are the following: Royal Marsden Hospital/Gloucester Oncology Center (RMH/GOC) Pilot Trial, Standardization of Breast Radiotherapy Trial A (START A), START B, and Randomized Trial of Breast Irradiation Schedules After Lumpectomy for Women With Lymph Node–Negative Breast Cancer (Canadian Trial).^{16–18} Each trial compared one or two HF-WBI test schedules to traditional SF-WBI of 50 Gy delivered over 25 consecutive weekdays in treatments of 2 Gy each (Fig 1). Together, these trials treated 6,582 women with WBI, of whom 4,159 were treated with HF-WBI (Table 1). Each trial has published results in peer-reviewed journals with follow-up of approximately 10 years.

Investigators at RMH/GOC initiated a three-arm randomized trial in 1986 comparing two HF-WBI treatment schedules to SF-WBI (Fig 1).¹⁶ The novelty of this first trial was use of larger doses per treatment in the experimental arms while keeping the total treatment time of 5 weeks constant. Thus, patients were not treated daily, but were treated 3, 2, 3, 2, and 3 times per week, respectively. The two HF-WBI dose arms delivered 39 Gy (3 Gy × 13) and 42.9 Gy (3.3 Gy × 13). Eligible patients were younger than age 75 years and were stratified by whether tumor was within 3 mm of the surgical margin. Treatment failure at 10 years was 12% in the 50-Gy arm, 15% in the 39-Gy arm, and 10% in the 42.9-Gy HF arm.¹⁷ There was no significant difference between the arms. Distant relapses, disease-free survival (DFS), and overall survival (OS) have not been reported.

Table 1. Key Components of Published Randomized Trials

Variable	RMH/GOC	START A	START B	Canadian	Total
Total No. of patients enrolled	1,410	2,236	2,215	1,234	7,095
Accrual years	1986-1998	1999-2002	1999-2002	1993-1996	
Median follow-up, years	9.7	9.3	9.9	12	
Stage	pT1-3N0-1M0	pT1-3aN0-1M0	pT1-3aN0-1M0	pT1-2N0M0	
Lumpectomy					
No.	1,410	1,900	2,038	1,234	6,582/7,092*
Percent	100	85	92	100	93
Treated with HF					
No.	940	1,487	1,110	622	4,159/6,582†
Percent					63
Treated with lumpectomy boost					
No.	1,051/1,410	1,159/1,900	876/2,038	0	3,086/6,582‡
Percent	75	61	43		47
Beam energies for breast, MV	6	6	6	Co60 or 4 to 6	

Abbreviations: Canadian, Randomized Trial of Breast Irradiation Schedules After Lumpectomy for Women with Lymph Node-negative Breast Cancer; Co60, Cobalt-60; HF, hypofractionation; RMH/GOC, Royal Marsden Hospital/Gloucester Oncology Center; START A, Standardization of Breast Radiotherapy Trial A; START B, Standardization of Breast Radiotherapy Trial B.

*Number of patients treated with lumpectomy/number of patients treated.

†Number of lumpectomy patients treated with HF/number of lumpectomy patients treated.

‡Number of lumpectomy patients treated with lumpectomy boost/number of lumpectomy patients treated.

Eligibility for both START A and START B was similar. Patients treated with mastectomy or those who would receive nodal irradiation were allowed, but these patients were a minority of those enrolled. Prerandomization stratification included treating center, type of local surgery (lumpectomy or mastectomy), and plan for delivery of tumor bed boost (10 Gy in five fractions). START A compared a standard fraction (SF) treatment course to two accelerated fractionation courses, each with 13 treatments spread over a 5-week period as in the RMH/GOC pilot trial. The START A test schedules intentionally kept 5 weeks of treatment constant, changing only the dose per treatment and number of treatments. Patients were assessed for locoregional relapse, even after distant treatment failure, an important measure when assessing the efficacy of local therapies. For the primary end point of locoregional failure (LRF) in START A, no significant difference was identified between the HF-WBI test arms (39 Gy and 41.6 Gy) and the SF-WBI control arm. DFS and OS were not significantly different between any of the START A treatment schedules.¹⁸

START B compared a traditional 50-Gy treatment schedule with 40 Gy in 15 fractions delivered on consecutive weekdays (3 weeks duration). Of those enrolled, 92% had breast-conserving surgery, 23% had positive lymph nodes, 22% received adjuvant chemotherapy, 87% received tamoxifen, and 7% were treated with nodal radiotherapy. There was no difference between the two treatment arms (SF-WBI v 40 Gy HF-WBI) for the primary end point of LRF. START B reported a surprising significant decrease in distant treatment failures in the 40-Gy arm compared with the SF arm, resulting in significantly higher DFS and OS rates in the HF arm.¹⁸

In the Canadian trial, SF was compared with 42.5 Gy in 16 treatments delivered over consecutive weekdays (or 3.2 weeks). Unlike the START trials, node-positive patients and those treated with mastectomy were not eligible for the Canadian trial; patients could not be treated with a lumpectomy boost or receive nodal irradiation. There was no difference in cumulative local recurrence between the two dose

schedules in the Canadian trial.¹⁹ At 10 years, local invasive recurrence was 7% in the standard arm versus 6% in the accelerated arm. Survival curves for the two arms of the Canadian trial are superimposable ($P = .79$), with 10-year OS rates of 84% in the SF arm and 85% in the HF arm.¹⁹ An unplanned subgroup analysis demonstrated equal efficacy of the two regimens, regardless of patient age, tumor size, estrogen receptor (ER) status, or use of systemic therapy. There was, however, a significantly worse local relapse rate in patients with high-grade tumors treated on the HF arm compared with the SF arm (16% v 5%). This interaction was not identified in a larger and statistically more powerful meta-analysis of the RMH/GOC and START trials.¹⁸

A summary of the use of lumpectomy boost in the HF-WBI trials is presented in Table 2. Approximately half the patients enrolled onto the RMH/GOC trial underwent a second random assignment for delivery of a boost or no boost, and the remaining patients were all given an elective boost. In this trial, no analysis was made comparing SF-WBI with boost to HF-WBI without boost. In both START trials, use of a boost (10 Gy in five fractions) was optional. The most recent START publication in 2013¹⁸ included a meta-analysis of patient data from RMH/GOC, START A, and START B. There was no difference in LRF between the SF-WBI and HF-WBI arms in a subgroup analysis of patients treated with a tumor bed boost. The meta-analysis for any moderate or marked physician-assessed normal tissue effects in the breast significantly favored the HF-WBI arms for patients who did and did not receive a tumor bed boost. These data from more than 3,000 patients with lengthy follow-up give adequate support for the equivalence in tumor control and improved late tissue effects for HF-WBI with boost compared with SF-WBI without boost. Although the American Society of Therapeutic Radiology and Oncology (ASTRO) guidelines state, "there were few data to define the . . . toxicity of a tumor bed boost in patients treated with HF-WBI," this guideline was published in 2011, before this most recent data became available.²⁰

Toxicity and Cosmesis

Major end points, including toxicity and cosmesis, are summarized in Table 3. Reported ischemic heart disease at 10 years for women treated in the START trials ranged between 1% and 2% without an appreciable difference between schedules. Similarly, death as a result of cardiac disease was low (4% to 7%) without an appreciable difference between fractionation regimens. In the RMH/GOC trial,¹⁶ there was a significant increase in shoulder stiffness in the 42.9-Gy arm but no effect on arm edema. In START A and START B, there were no apparent differences or trends between arms for these end points. Symptomatic rib fracture and symptomatic lung fibrosis in START A and START B occurred at an extremely low rate by 10 years without an apparent difference between schedules. No differences in toxicity were identified in the Canadian trial.

Together, the randomized trials establish that HF-WBI in the dose schedules evaluated not only maintain cosmesis but may even improve it compared with SF therapy. In the RMH/GOC trial, there were significant differences between the treatment schedules with regard to fair and/or poor cosmesis, breast shrinkage, breast distortion, breast induration, and breast edema. The difference for development of telangiectasia was of borderline significance ($P = .07$). Although statistical comparisons between any two arms were not made, there was less toxicity for each end point in the 39-Gy arm compared with the 50-Gy arm.

In START A, the lower dose 39-Gy arm had significantly less breast induration, telangiectasia, and breast edema compared with the 50-Gy arm. There were no trends or significant differences in cosmetic end points between the higher-dose 41.6-Gy and 50-Gy arms. Cosmesis end points were improved for the accelerated arm in START B for physician-assessed end points with regard to breast shrinkage, breast edema, and telangiectasia. In the Canadian trial, no significant differences between the two treatment arms were identified at any time. An excellent-good cosmetic outcome was described in approximately 70% of patients in each arm. Late skin and subcutaneous tissue toxicity did not differ between treatment arms at 5 or 10 years.

Ductal Carcinoma In Situ, Cost, and HF-WBI Guidelines

Several multi-institutional retrospective trials²¹⁻²³ and single-institution prospective trials²⁴ have demonstrated outcomes after HF-WBI for ductal carcinoma in situ (DCIS) that appear equivalent to traditional SF-WBI schedules: 5-year local recurrence rates of 3% to 7%. BIG 3-07/TROG 07.01 (A Randomised Phase III Study of Radiation Doses and Fractionation Schedules for Ductal Carcinoma In Situ [DCIS] of the Breast, by the Breast International Group [BIG] and the Trans Tasman Radiation Oncology Group [TROG]) is currently accruing to a 2 × 2 randomized trial for DCIS: SF versus HF (43.5 Gy in 16 fractions) and no boost versus boost (10 Gy in five fractions).²⁵ The trial has accrued 84% of its global target accrual of 1,600 patients as of December 2013.²⁶

A major component of cost in radiation therapy is the number of treatments delivered.²⁷ An SF treatment course was recently estimated to cost \$13,359 and an HF course (16 fractions) was \$9,122 based on US 2011 Medicare reimbursement rates.²⁸ Others costs more difficult to quantify are lost wages and travel costs, which would also be reduced by use of HF schedules. The decrease in reimbursement associated with shorter HF schedules is likely a contributing factor to the

relatively slower adoption of these treatment schedules in the US fee-for-service system.

ASTRO published an evidence-based guideline²⁰ for use of HF-WBI in 2011. The document offers support for HF-WBI, noting equivalence in tumor control and toxicity when compared with SF therapy; the panel reached 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%. The document states that lack of consensus in support of HF-WBI for patients who do not meet all these criteria “should not be interpreted as a contraindication to its use.”

“Choosing Wisely” is an initiative of the American Board of Internal Medicine²⁹ in which medical specialty societies are asked to identify tests or procedures whose necessity should be questioned. The campaign encourages conversations between patients and physicians that result in care decisions that are “supported by evidence, not duplicative of other tests or procedures already received, free from harm, and truly necessary.” In 2013, ASTRO identified fractionation in WBRT as one of its issues for the Choosing Wisely initiative.³⁰ ASTRO encourages consideration of shorter fractionation schedules for women age 50 years or older with early-stage breast cancer. The recent National Comprehensive Cancer Network guideline for breast cancer uses language that is neutral to the selection of SF-WBI or HF-WBI treatment regimens.³¹

APBI

Even briefer than the HF-WBI schedules already described are those used for APBI, which focuses radiation to the 1 to 2 cm of tissue surrounding the lumpectomy bed, considered to be the tissue at highest risk of containing residual tumor cells following breast-conserving surgery. This approach combines a treatment volume question (Can APBI yield tumor control rates equivalent to WBI?) and a fractionation question (Can fewer treatments delivering larger doses per treatment yield equivalent tumor and toxicity rates?).

RTOG-9517 (A Phase I/II Trial to Evaluate Brachytherapy As the Sole Method of Radiation Therapy for Stage I and II Breast Carcinoma) evaluated multicatheter APBI in a phase II trial with either low-dose-rate therapy of 45 Gy over 5 to 7 days or 34 Gy in 10 twice-per-day treatments of 3.4 Gy each. Long-term results demonstrate durable breast tumor control of 94% at 10 years.³² Specialized devices were developed to provide simpler methods of APBI brachytherapy delivery, all of which allowed for placement of the device into the operative cavity, either during the surgical procedure immediately following lumpectomy or days later after confirmation of pathology. External-beam APBI has also been examined; the small phase II RTOG-0319 trial (Three-Dimensional Conformal Radiation Therapy [3D-CRT] Confined to the Region of the Lumpectomy Cavity for Stage I/II Breast Carcinoma) in which treatment of 52 analyzable patients with 38.5 Gy in 10 twice-per-day fractions yielded a breast tumor control rate of 92.3% at 7 years.³³

Randomized trials comparing SF-WBI and APBI are maturing. A Hungarian trial of 258 patients yielded 5-year breast control rates of 97% for SF-WBI versus 95% for APBI.³⁴ A trial by the Yorkshire Breast Cancer Group met with accrual difficulties and closed after enrolling 174 patients; results suggested higher local failure rates with APBI.³⁵

Table 2. Trials Using Lumpectomy Bed Boost

Variable	RMH/GOC	START A	START B	Total
Total No. of patients enrolled	1,410	2,236	2,215	5,861
Lumpectomy				
No.	1,410	1,900	2,038	5,348
Percent	100	85	92	
Treated with boost/lumpectomy				
No.	1,051/1,410	1,159/1,900	876/2,038	3,086/5,348
Percent	75	61	43	58
Boost policy	Second randomization for part of trial	Stratification factor; with or without boost declared prerandomization	Stratification factor; with or without boost declared prerandomization	
Nonrandomized boost	687	1,159	876	2,722
Boost dose	14 Gy (2 Gy × 7)	10 Gy (2 Gy × 5)	10 Gy (2 Gy × 5)	

Abbreviations: RMH/GOC, Royal Marsden Hospital/Gloucester Oncology Center; START A, Standardization of Breast Radiotherapy Trial; START B, Standardization of Breast Radiotherapy Trial B.

Larger trials adequately powered to demonstrate meaningful differences or noninferiority in tumor control rates have yet to be published. The Canadian RAPID trial (RAPID: Randomized Trial of Accelerated Partial Breast Irradiation) enrolled 2,135 women and compared SF-WBI to external-beam three-dimensional conformal APBI (38.5 Gy in 10 twice-per-day fractions); this trial closed to accrual in 2011.³⁶ Although final outcomes of this trial will not be available for several years, a recent mandated interim toxicity analysis demonstrated inferior cosmetic outcome in the APBI arm assessed by three independent measures, including patient assessment, nurse assessment, and physician assessment. While further follow-up and analysis of this and other studies is awaited, these results raise some concerns regarding the long-term cosmesis associated with this hypofractionated external-beam radiation scheme.^{37,38} NSABP B-39/RT0G 0413 (A Randomized Phase III Study of Conventional Whole Breast Irradiation [WBI] Versus Partial Breast Irradiation [PBI] for Women With Stage 0, I, or II Breast Cancer) enrolled 4,311 patients and compared SF-WBI with APBI using any of the three techniques (multicatheter, intracavitary, or external beam) described earlier.⁴⁰ This trial closed to accrual in 2013. Results of these latter two trials will be essential to meaningfully identify the efficacy and toxicity of APBI.

IORT

IORT was developed to reduce even further the logistical burden of radiation treatment and to deliver dose directly to the tumor bed, integrating the surgical and radiation care. In-breast treatment failures following lumpectomy account for the vast majority of local recurrences.⁴¹⁻⁴³ To test the hypothesis that treating the tumor bed focally with radiotherapy during surgery would lead to noninferior breast recurrence outcomes, the TARGIT-A (Targeted Intraoperative Radiotherapy) trial was opened. Women age 45 years or older with unifocal nonlobular breast cancer suitable for breast-conserving surgery were eligible. Two arms were randomly assigned, including a prepathology arm with treatment assigned before lumpectomy and a postpathology arm with wound reopening if the patient was assigned to the IORT arm. Treatment with IORT was delivered by using low-energy x-rays (50 kV maximum) via a point source at the tip of a tube inside a spherical applicator placed in the lumpectomy bed. The lumpectomy bed surface was then treated to 20 Gy, with rapid atten-

uation in the surrounding tissue (5 to 7 Gy at 1 cm), leading to an extremely focal high-dose therapy.⁴⁴

Five-year results demonstrate that 15% of patients in the prepathology arm met criteria for subsequent external-beam WBI based on predefined pathologic criteria. Five-year local recurrence was significantly higher with IORT, although both arms had modest recurrence rates at 3% with IORT and 1% with WBI. Noninferiority was confirmed in the prepathology arm but not in the postpathology arm. Breast cancer mortality and OS were not significantly different between the groups. Serious skin complications were significantly reduced with IORT compared with external beam WBI, with both arms lower than 1%. No difference in wound complications was seen.⁴⁵

The ELIOT trial (Intraoperative Radiotherapy Versus External Radiotherapy for Early Breast Cancer: A Randomised Controlled Equivalence Trial) used electrons (intraoperative electron radiation therapy [IOERT]) rather than the photon technique described earlier. This randomized study included women older than age 48 years with unifocal infiltrating carcinoma up to 2.5 cm in diameter. The treatment arms used either 50 Gy WBI and 10 Gy lumpectomy bed boost using external beam radiation or a single dose of IOERT to 21 Gy at the 90% isodose line (Table 2).⁴⁶ The initial results of the study underscored the importance of a robust quality assurance program.⁴⁷ The 5-year results from this study demonstrate that IOERT must be approached with caution, because the IOERT arm was inferior. The 5-year local recurrence rates were 1% on the conventional arm and 5% on the IOERT arm ($P < .001$). The authors concluded that IOERT requires careful patient selection and careful quality assurance, because noninferiority was not demonstrated.⁴⁸

APBI Guidelines

In 2009, ASTRO published guidelines for APBI outside a randomized trial.²⁰ Patients considered suitable included women age 60 years or older with unicentric T1N0 ER-positive invasive breast cancers resected with negative surgical margins of 2 mm or more. Caution or concern should be invoked with any of the following features: age 50 to 59 years, T0 (pure DCIS), T2, ER-negative status, margins less than 2 mm, lymphovascular space invasion, and extensive intraductal component. All other patients are considered unsuitable for APBI.

Table 3. Comparison of HF to SF With Regard to Major End Points at 10 Years

10-Year Event	RMH/GOC			START A			START B			Canadian			
	Arm (Gy)	Result (%)	P	Arm (Gy)	Result (%)	P	Arm (Gy)	Result (%)	P	Arm (Gy)	Result (%)	P	
Ipsilateral breast tumor relapse	50	12.1	.027	50	6.7	NS	50	3.8	NS	50	7.4	NS	
	42.9	9.6		41.6	5.6		40	5.2		42.5	7.5		
	39	14.8		39	8.1								
Distant relapse	NR			50	14.7	NS	50	16.0	.014	NR			
				41.6	16.8		40	12.3					
				39	18.0								
All-cause mortality	NR			50	19.8	NS	50	19.2	.042	50	15.6	NS	
				41.6	18.4		40	15.9		42.5	15.4		
				39	20.3								
Cosmesis, selected end points				Telangiectasia						Excellent-Good			
	50	18.1	.065	50	7.2	—	50	5.8	.032	42.5	69.8	NS	
	42.9	18.0		41.6	7.1		.99	40		4.2	50		71.3
	39	12		39	3.0		.003						
				Breast Edema									
	50	13.8	.004	50	13.5		50	9.0	.001				
	42.9	21.5		41.6	11.8		.24	40		5.1			
	39	11.5		39	7.3		.001						
	Toxicity, selected end points				Ischemic Heart Disease						Grade 3 Skin		
			50	1.9		50	2.1		42.5	2.7	NS		
			41.6	1.5		40	1.5		50	2.5			
			39	1.1									
			Symptomatic Lung Fibrosis						Grade 3 Subcutaneous Tissue				
			50	1.2		50	1.7		42.5	3.6	NS		
			41.6	1.1		40	1.7		50	2.5			
			39	1.0									
Abbreviations: HF, hypofractionation; NR, not reported; NS, not significant; RMH/GOC, Royal Marsden Hospital/Gloucester Oncology Center; SF, standard fractionation; START A, Standardization of Breast Radiotherapy Trial A; START B, Standardization of Breast Radiotherapy Trial B.													

Abbreviations: HF, hypofractionation; NR, not reported; NS, not significant; RMH/GOC, Royal Marsden Hospital/Gloucester Oncology Center; SF, standard fractionation; START A, Standardization of Breast Radiotherapy Trial A; START B, Standardization of Breast Radiotherapy Trial B.

FUTURE DIRECTIONS

One of the next logical steps in shortening radiotherapy treatment courses for early-stage breast cancer is to use the advantages of standard yet sophisticated planning and treatment systems to integrate additional doses into the lumpectomy bed during the delivery of WBI (integrated boost). This approach has been evaluated by several institutions, and it demonstrates good efficacy and minimal toxicity, albeit in retrospective or phase II trials.³²⁻³⁷ These treatment approaches vary from integration of a boost into SF-WBI to HF-WBI courses of 3 to 4 weeks. RTOG 1005 (A Phase III Trial of Accelerated Whole Breast Irradiation With Hypofractionation Plus Concurrent Boost Versus Standard Whole Breast Irradiation Plus Sequential Boost for Early-Stage Breast Cancer) is a randomized trial currently accruing patients to evaluate the use of an integrated boost.⁴⁰

With the excellent outcomes in HF-WBI schedules over 3 to 3.2 weeks, HF-WBI schedules of shorter duration or fewer fractions would be attractive if similar efficacy and toxicity could be demonstrated. Shorter HF-WBI schedules would provide further convenience, efficiency of resources, and cost savings. To explore this issue, the United Kingdom FAST Trial (Randomised UK FAST Trial of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer (CRUKE/04/015))^{49,50} enrolled women age 50 years or older with node-negative breast cancer. Women were randomly assigned to one of three WBI treatment arms: SF, 28.5 Gy in five once-per-week fractions, or

30 Gy in five once-per-week fractions (Fig 1). Three-year rates of any moderate or adverse breast effects were similar in the SF-WBI and 28.5-Gy arm but significantly worse in the 30-Gy arm compared with either of the other two arms. The trial was not powered to compare rates of breast tumor control between schedules. Building on the United Kingdom FAST Trial, FAST-Forward (Randomised Clinical Trial Testing a One Week Course of Curative Whole Breast Radiotherapy Against a Standard Three Week Schedule in Terms of Local Cancer Control and Late Adverse Effects in Patients With Early Breast Cancer)⁵¹ is comparing HF-WBI (40 Gy in 15 fractions) to two 1-week schedules of 26 to 27 Gy. The primary end point is ipsilateral breast tumor control, and secondary end points include late adverse effects in normal tissues.

There are fewer data on the use of HF-WBI in the treatment of DCIS, the postmastectomy patient, and inclusion of regional nodal basins. SF-WBI approaches will continue as the norm for these patients in the United States until randomized data evaluating HF-WBI for these settings becomes available. An international trial evaluating HF-WBI for DCIS is currently ongoing.⁵²

CONCLUSION

The use of adjuvant radiotherapy as a component of breast-conserving therapy originated nearly a century ago and remains an integral part of the management of early-stage breast cancer, offering most patients an opportunity to achieve durable tumor control and an excellent

cosmetic outcome that promotes a sense of wholeness and well-being. Clinical research to refine the radiotherapy methodology used for this purpose remains one of the most vibrant areas of investigation within the field. In the modern era in which the need to use health care resources efficiently has become a top priority, studies comparing older strategies to newer, more efficient treatment schedules serve as model studies that demonstrate opportunities for cost savings in some settings without compromise to tumor control or quality outcomes. It can be argued that HF-WBI is now the preferred standard of care for the reasons cited earlier.⁵³ ASTRO's encouragement of HF-WBI in the Choosing Wisely campaign is intended to promote more widespread dissemination of this treatment mode in the coming years.

REFERENCES

1. Medvei VC: The History of Clinical Endocrinology: A Comprehensive Account of Endocrinology from Earliest Times to the Present Day. New York, NY, The Parthenon Publishing Group, 1993
2. Keynes G: A Study of the Illuminated Books of William Blake: Poet, Printer, Prophet. New York, NY, Orion Press with Trianon Press, 1964
3. Keynes G: Conservative treatment of cancer of the breast. *BMJ* 2:643-666, 1937
4. Keynes G: Radium treatment of primary carcinoma of the breast. *Lancet* 212:108-111, 1928
5. Prosnitz LR, Goldenberg IS: Radiation therapy as primary treatment for early stage carcinoma of the breast. *Cancer* 35:1587-1596, 1975
6. Prosnitz LR, Goldenberg IS, Packard RA, et al: Radiation therapy as initial treatment for early stage cancer of the breast without mastectomy. *Cancer* 39:917-923, 1977
7. Weber E, Hellman S: Radiation as primary treatment for local control of breast carcinoma: A progress report. *JAMA* 234:608-611, 1975
8. Fisher B, Anderson S, Bryant J, et al: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 347:1233-1241, 2002
9. Veronesi U, Luini A, Del Vecchio M, et al: Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 328:1587-1591, 1993
10. Blichert-Toft M, Rose C, Andersen JA, et al: Danish randomized trial comparing breast conservation therapy with mastectomy: Six years of life-table analysis—Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr* 11:19-25, 1992
11. van Dongen JA, Voogd AC, Fentiman IS, et al: Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 92:1143-1150, 2000
12. Jacobson JA, Danforth DN, Cowan KH, et al: Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med* 332:907-911, 1995
13. Sarrazin D, Lê MG, Arriagada R, et al: Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncol* 14:177-184, 1989

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Rachel Rabinovitch

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

14. Kavanagh BD, Miften M, Rabinovitch RA: Advances in treatment techniques: Stereotactic body radiation therapy and the spread of hypofractionation. *Cancer J* 17:177-181, 2011
15. Timmerman RD, Kavanagh BD, Cho LC, et al: Stereotactic body radiation therapy in multiple organ sites. *J Clin Oncol* 25:947-952, 2007
16. Yarnold J, Ashton A, Bliss J, et al: Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: Long-term results of a randomised trial. *Radiother Oncol* 75:9-17, 2005
17. Owen JR, Ashton A, Bliss JM, et al: Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: Long-term results of a randomised trial. *Lancet Oncol* 7:467-471, 2006
18. Haviland JS, Owen JR, Dewar JA, et al: The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 14:1086-1094, 2013
19. Whelan TJ, Pignol JP, Levine MN, et al: Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 362:513-520, 2010
20. Smith BD, Bentzen SM, Correa CR, et al: Fractionation for whole breast irradiation: An American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys* 81:59-68, 2011
21. Williamson D, Dinniwell R, Fung S, et al: Local control with conventional and hypofractionated adjuvant radiotherapy after breast-conserving surgery for ductal carcinoma in-situ. *Radiother Oncol* 95:317-320, 2010
22. Hathout L, Hjal T, Théberge V, et al: Hypofractionated radiation therapy for breast ductal carcinoma in situ. *Int J Radiat Oncol Biol Phys* 87:1058-1063, 2013
23. Wai ES, Lesperance ML, Alexander CS, et al: Effect of radiotherapy boost and hypofractionation on outcomes in ductal carcinoma in situ. *Cancer* 117:54-62, 2011
24. Ciervide R, Dhage S, Guth A, et al: Five year outcome of 145 patients with ductal carcinoma in situ (DCIS) after accelerated breast radiotherapy. *Int J Radiat Oncol Biol Phys* 83:e159-e164, 2012
25. Trans Tasman Radiation Oncology Group: BIG 3-07: A randomised phase III study of radiation doses and fractionation schedules for ductal carcinoma in situ (DCIS) of the breast. <http://www.rtrialsqa.org.uk/rtrtq/?q=big3-07>
26. UK Clinical Research Network Study Portfolio: BIG 3-07 (TROG 07.01) A Randomised Phase III Study of Radiation Doses and Fractionation Schedules for Ductal

- Carcinoma In Situ (DCIS) of the Breast. <http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=8971>
27. Lievens Y: Hypofractionated breast radiotherapy: Financial and economic consequences. *Breast* 19:192-197, 2010
28. Greenup RA, Camp MS, Taghian AG, et al: Cost comparison of radiation treatment options after lumpectomy for breast cancer. *Ann Surg Oncol* 19:3275-3281, 2012
29. American Board of Internal Medicine: Choosing Wisely. <http://www.abimfoundation.org/Initiatives/Choosing-Wisely.aspx>
30. American Board of Internal Medicine: Choosing Wisely: ASTRO Releases List of Five Radiation Oncology Treatments to Question As Part of National Choosing Wisely Campaign. <http://www.choosingwisely.org/astro-releases-list-of-five-radiation-oncology-treatments-to-question-as-part-of-national-choosing-wisely-campaign/>
31. National Comprehensive Cancer Network (NCCN): NCCN Clinical Practice Guidelines in Oncology: Breast Cancer version 3.2014. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
32. Chadha M, Woode R, Sillanpaa J, et al: Early-stage breast cancer treated with 3-week accelerated whole-breast radiation therapy and concomitant boost. *Int J Radiat Oncol Biol Phys* 86:40-44, 2013
33. Formenti SC, Gidea-Addeo D, Goldberg JD, et al: Phase I-II trial of prone accelerated intensity modulated radiation therapy to the breast to optimally spare normal tissue. *J Clin Oncol* 25:2236-2242, 2007
34. McDonald MW, Godette KD, Whitaker DJ, et al: Three-year outcomes of breast intensity-modulated radiation therapy with simultaneous integrated boost. *Int J Radiat Oncol Biol Phys* 77:523-530, 2010
35. Cante D, Franco P, Sciacero P, et al: Five-year results of a prospective case series of accelerated hypofractionated whole breast radiation with concomitant boost to the surgical bed after conserving surgery for early breast cancer. *Med Oncol* 30:518, 2013
36. Freedman GM, Anderson PR, Goldstein LJ, et al: Four-week course of radiation for breast cancer using hypofractionated intensity modulated radiation therapy with an incorporated boost. *Int J Radiat Oncol Biol Phys* 68:347-353, 2007
37. Olivetto IA, Whelan TJ, Parpia S, et al: Interim cosmetic and toxicity results from RAPID: A randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol* 31:4038-4045, 2013
38. Jaggi R, Haffty BG: External-beam accelerated partial-breast irradiation: Exploring the limits of tolerability. *J Clin Oncol* 31:4029-4031, 2013

39. Scorsetti M, Alongi F, Fogliata A, et al: Phase I-II study of hypofractionated simultaneous integrated boost using volumetric modulated arc therapy for adjuvant radiation therapy in breast cancer patients: A report of feasibility and early toxicity results in the first 50 treatments. *Radiat Oncol* 7:145, 2012
40. Radiation Therapy Oncology Group: RTOG 1005 Protocol Information. <http://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?study=1005>
41. Schnitt SJ, Connolly JL, Harris JR, et al: Pathologic predictors of early local recurrence in Stage I and II breast cancer treated by primary radiation therapy. *Cancer* 53:1049-1057, 1984
42. Clark RM, Wilkinson RH, Mahoney LJ, et al: Breast cancer: A 21 year experience with conservative surgery and radiation. *Int J Radiat Oncol Biol Phys* 8:967-979, 1982
43. Fisher ER, Anderson S, Redmond C, et al: Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: Pathological findings from NSABP protocol B-06. *Semin Surg Oncol* 8:161-166, 1992
44. Vaidya JS, Joseph DJ, Tobias JS, et al: Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): An international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 376:91-102, 2010
45. Vaidya JS, Wenz F, Bulsara M, et al: Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 383:603-613, 2014
46. Orecchia R, Ciocca M, Lazzari R, et al: Intraoperative radiation therapy with electrons (ELIOT) in early-stage breast cancer. *Breast* 12: 483-490, 2003
47. Orecchia R, Ciocca M, Tosi G, et al: Intraoperative electron beam radiotherapy (ELIOT) to the breast: A need for a quality assurance programme. *Breast* 14:541-546, 2005
48. Veronesi U, Orecchia R, Maisonneuve P, et al: Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. *Lancet Oncol* 14:1269-1277, 2013
49. FAST Trialists group, Agrawal RK, Alhasso A, et al: First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). *Radiother Oncol* 100:93-100, 2011
50. Institute of Cancer Research (ICR): FAST-Forward: Randomised Clinical Trial Testing a 1-Week Course of Curative Whole Breast Radiotherapy Against a Standard 3-Week Schedule in Terms of Local Cancer Control and Late Adverse Effects in Patients With Early Breast Cancer. http://www.icr.ac.uk/research/research_divisions/Clinical_Studies/Clinical_Trials/Clinical_Trials_Disease/CT_Disease_Breast/fast_forward/22304.shtml
51. UK Clinical Research Network Study Portfolio: FAST-Forward Study. <http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=10896>
52. Trans Tasman Radiation Oncology Group (TROG): TROG trial 07.01 (DCIS): Radiation Doses and Fractionation Schedules in Non-Low Risk Ductal Carcinoma In Situ (DCIS) of the Breast. <http://www.trog.com.au/TROG-0701-DCIS>
53. Haffty BG, Buchholz TA: Hypofractionated breast radiation: Preferred standard of care? *Lancet Oncol* 14:1032-1034, 2013