

Scientific Article

Adoption of Ultrahypofractionated Radiation Therapy in Patients With Breast Cancer



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Abstract

Introduction: The first high-quality clinical trial to support ultrahypofractionated whole-breast irradiation (ultra-HF-WBI) for invasive early-stage breast cancer (ESBC) was published in April 2020, coinciding with the beginning of the COVID-19 pandemic. We analyzed adoption of ultra-HF-WBI for ductal carcinoma in situ (DCIS) and ESBC at our institution after primary trial publication.

Methods and Materials: We evaluated radiation fractionation prescriptions for all patients with DCIS or ESBC treated with WBI from March 2020 to May 2021 at our main campus and regional campuses. Demographic and clinical characteristics were extracted from the electronic medical record. Treating physician characteristics were collected from licensure data. Hierarchical logistic regression models identified factors correlated with adoption of ultra-HF-WBI (26 Gy in 5 daily fractions [UK-FAST-FORWARD] or 28.5 Gy in 5 weekly fractions [UK-FAST]).

Results: Of 665 included patients, the median age was 61.5 years, and 478 patients (71.9%) had invasive, hormone-receptor-positive breast cancer. Twenty-one physicians treated the included patients. In total, 249 patients (37.4%) received ultra-HF-WBI, increasing from 4.3% (2 of 46) in March-April 2020 to a high of 45.5% (45 of 99) in July-August 2020 ($P < .001$). Patient factors associated with increased use of ultra-HF-WBI included older age (≥ 50 years old), low-grade WBI without inclusion of the low axilla, no radiation boost, and farther travel distance ($P < .03$). Physician variation accounted for 21.7% of variance in the outcome, with rate of use of ultra-HF-WBI by the treating physicians ranging from 0% to 75.6%. No measured physician characteristics were associated with use of ultra-HF-WBI.

Conclusions: Adoption of ultra-HF-WBI at our institution increased substantially after the publication of randomized evidence supporting its use. Ultra-HF-WBI was preferentially used in patients with lower risk disease, suggesting careful selection for this new

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approach while long-term data are maturing. Substantial physician-level variation may reflect a lack of consensus on the evidentiary standards required to change practice.

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Introduction

Historically, patients with ductal carcinoma in situ (DCIS) or invasive early-stage breast cancer (ESBC) requiring radiation therapy were treated with conventionally fractionated whole-breast irradiation (CF-WBI) regimens of approximately 50 to 50.4 Gy in 25 to 28 daily treatments with or without a sequential boost. In the past 20 years, many clinical trials investigated modestly hypofractionated schedules for whole-breast irradiation (HF-WBI) to shorten the total radiation treatment period. The Canadian¹ and United Kingdom START-B² trials compared CF-WBI with regimens of 42.5 Gy in 16 fractions and 40 Gy in 15 fractions, respectively. These studies demonstrated equal or superior local control, toxic effects, and cosmetic outcomes compared with CF-WBI.^{1,2} Subsequently, the FAST Trial Management Group took a substantial step forward in evaluating ultrahypofractionated (ultra-HF-WBI) regimens of 30 or 28.5 Gy in once-weekly treatments over 5 weeks in the UK-FAST (UK-F) trial³ and 27 or 26 Gy in 5 daily fractions over 1 week in the UK-FAST-FORWARD (UK-FF) trial.⁴ The UK-F and UK-FF studies showed that regimens of 28.5 Gy in 5 fractions over 5 weeks and 26 Gy in 5 fractions over 1 week were noninferior to CF-WBI³ and the earlier investigated HF-WBI regimen of 40 Gy in 15 fractions, respectively.⁴ Altogether, these studies indicated that both modest hypofractionation and ultra-HF-WBI are safe and efficacious for treating patients with WBI for invasive ESBC.

Despite the promising findings of the aforementioned trials, several studies have shown that there is a delay from publication of trial results to use of novel radiation fractionation regimens in clinical practice.⁵⁻⁸ This may be partially due to skepticism of trial results, desire for longer-term data follow-up, the delay in information flow from academic to community centers, and infrastructural and financial challenges.⁹ However, unique circumstances over the past year, including a global pandemic and publications from leaders in the field,¹⁰ may have accelerated the adoption of ultra-HF-WBI. The purpose of this study was to analyze the adoption of the recently published UK-F and UK-FF regimens for DCIS and ESBC patients at 1 large academic cancer center and its regional campuses. By analyzing the breast cancer fractionation patterns used at our institution, and specifically within our large practice specializing in breast radiation therapy, we aimed to uncover trends and gaps that could be informative for other institutions and future clinical practice.

Methods and Materials

To evaluate the patterns of WBI fractionation used at our institution, we identified patients with DCIS or invasive ESBC who were treated with WBI at our main campus or 4 community-based, fully integrated regional campuses from March 1, 2020, to May 19, 2021. All treating physicians were salaried, full-time faculty members at The University of Texas MD Anderson Cancer Center. The start date was chosen to provide 2 months of fractionation data before the UK-FF trial results were published. All patients were treated with external-beam photon therapy using 3-dimensional conformal or intensity modulated radiation therapy techniques. Patients receiving radiation therapy to the whole breast with or without the low axilla were included in the analysis; patients treated with a third field to cover the nodal basins were not included. Patients were excluded if they were treated with partial-breast irradiation (PBI) or proton therapy or if the bilateral breasts were treated concurrently.

Demographic and treatment characteristics for included patients were extracted from the electronic medical record. We selected factors related to the eligibility criteria in the UK-FF trial: women or men aged ≥ 18 years with invasive ESBC (pT1-T3, pN0-1, M0) after breast-conserving surgery or mastectomy.⁴ We extracted the following characteristics: age, race, histology (DCIS vs invasive cancer), receptor subtype (only for invasive cancer), pathologic T and N stage, tumor grade, breast cancer treatment site (whole breast only or with low axilla), receipt of chemotherapy (none, neoadjuvant, or adjuvant), radiation treatment period (in 2-month increments), radiation boost (no or yes), patients' distance to the hospital in miles (<25, 25-49, 50-149, 150-499, ≥ 500 , or international), and insurance (managed care, Medicare, government, Medicaid, self-pay, or other). Subtypes for invasive breast cancer included hormone receptor positive (HR+) (estrogen receptor [ER] positive or progesterone receptor [PR] positive and not HER2 positive), HER2 positive (regardless of ER/PR status), and triple negative (TN, ER/PR/HER2 negative). Attending physician characteristics included sex, race and ethnicity, year of medical school graduation (<2000, 2000-2004, 2005-2009, ≥ 2010), annual breast cancer patient volume (≤ 40 , 41-100, or >100 patients), academic rank (assistant professor, associate professor, or professor), whether they worked with rotating residents at least once annually, number of treating cancer sites (1 or >1), and practice location

(main hospital campus vs regional campus). Attending physicians who practice at the main hospital campus do not staff the regional campuses and vice versa; however, centralized quality assurance review of each patient was performed between the main campus and all regional campuses during the study period.

We tabulated baseline patient, clinical, and physician characteristics for all patients and stratified by 4 radiation regimens: UK-F (28.5 Gy in 5 weekly fractions), UK-FF (26 Gy in 5 daily fractions), Canadian/START-B (40-42.5 Gy in 15-16 fractions), and conventional (45-50.4 Gy in 25-28 fractions). Groups were compared using the χ^2 test. Hierarchical logistic regression accounted for clustering of patients nested within treating physicians. We tested the association of each patient's and treating physician's factors with the use of ultra-HF-WBI (UK-F or UK-FF). Patient and physician characteristics with univariate $P < .20$ were candidates for the multivariable model. Backward reduction was used to retain variables that had statistical significance in the final model. We expressed the results with risk ratios (RRs) and 95% confidence intervals (CIs) per the method by Zhang et al.¹¹ In addition, we estimated the variance partition coefficient accounted for by attending physicians to determine the proportion of the variance of the outcome attributable to attending physicians.¹² For multivariable analyses, we excluded physicians who treated 4 or fewer patients with breast cancer annually for stability of the estimates. We considered $P < .05$ statistically significant; all tests were 2-sided. Statistical analyses were carried out using SAS, version 9.4 (SAS Institute Inc, Cary, NC). This study was approved by our institutional review board.

Results

Baseline characteristics

We included 665 patients with DCIS or ESBC who were treated with WBI at our institution between March 2020 and May 2021 (Table 1). The median patient age was 61.5 years (range, 22-98 years). A majority of the patients (422 [63.5%]) identified as White, non-Hispanic; 103 (15.5%) identified as Hispanic (any race), 93 (14%) as Black, non-Hispanic, and 47 (7.1%) as other race or ethnicity. A total of 478 (71.9%) were diagnosed with invasive HR+ breast cancer, and 101 (15.2%) had DCIS. A total of 427 (64%) received a radiation boost, and 68 (10.2%) received WBI that intentionally included the low axillary lymph nodes. A majority (410 [61.6%]) lived within a 50-mile radius of the main hospital campus.

Twenty-one attending physicians treated the patients included in this analysis (Table 2). A majority of these

physicians identified as female (13 [61.9%]) and as White, non-Hispanic race (12 [57.1%]). Three physicians (14.3%) identified as Black, non-Hispanic, 3 (14.3%) as Asian, 2 (9.5%) as Hispanic, and 1 (4.8%) as American Indian or Alaska Native, non-Hispanic. Eight physicians (38.1%) held the academic rank of professor, 8 (38.1%) were associate professors, and 5 (23.8%) were assistant professors. Eleven physicians (52.4%) practiced at the main hospital campus and 10 (47.6%) practiced at regional campuses in the greater metropolitan area. Eleven physicians (52.4%) exclusively treated patients with breast cancer.

Adoption of ultra-HF-WBI

A total of 249 patients (37.4%) were treated with ultra-HF-WBI: 231 (34.7%) with UK-FF and 18 (2.7%) with UK-F. A total of 416 patients (62.6%) were treated with other regimens: 401 (60.3%) with Canadian/START-B and 15 (2.3%) with a conventional regimen. Use of UK-FF increased over time (Fig 1), from 2 of 46 patients (4.3%) in March-April 2020 to 36 of 95 (37.9%) in May-June 2020 and a high of 45 of 99 (45.5%) in July-August 2020 ($P < .05$). Use remained elevated compared with baseline throughout the remainder of the study period.

Patient-level predictors of ultra-HF-WBI

Multivariable analysis identified several key patient-level factors associated with receipt of ultra-HF-WBI regimens. For example, there were statistically significant associations between older age (≥ 50 years) and receipt of ultra-HF-WBI and low-grade WBI and (Table 3). Additionally, patients with radiation treatment plans that did not include a boost (RR, 1.97; 95% CI, 1.55-2.38; $P < .001$) or did not include the low axilla (RR, 2.65; 95% CI, 1.62-3.73; $P = .004$) were more likely to receive ultra-HF-WBI. Patients who traveled a farther distance from their home to the hospital were also more likely to receive ultra-HF-WBI (travel distance of 50-149 miles: RR, 1.51; 95% CI, 1.05-1.99; $P = .03$; for ≥ 150 miles: RR, 1.92; 95% CI, 1.45-2.35; $P < .001$).

Physician-level predictors of ultra-HF-WBI

Among the 16 attending physicians who treated at least 10 patients with breast cancer annually (median, 76 patients; range, 16-107 patients), use of the ultra-HF-WBI regimens varied widely, from 0% to 75.6% (Fig 2). In multivariate analysis, 21.7% of the variance in use of ultra-HF-WBI partitioned to the physician level. In the multivariable adjusted model, there were no physician-level characteristics, including sex, race,

Table 1 Patient demographic and clinical characteristics (N = 665)^a

Characteristic	Total, n (%)	UK-FAST FORWARD, n (%)	UK-FAST, n (%)	Canadian/ START-B, n (%)	Conventional, n (%)	P value
Age, y						
18-49	121 (18.2)	16 (6.9)	1 (5.6)	97 (24.2)	7 (46.7)	<.001
50-59	172 (25.9)	46 (19.9)	3 (16.7)	119 (29.7)	4 (26.7)	
60-69	242 (36.4)	99 (42.9)	8 (44.4)	131 (32.7)	4 (26.7)	
70 or older	130 (19.5)	70 (30.3)	6 (33.3)	54 (13.5)	0	
Sex						
Female	663 (99.7)	229 (99.1)	18 (100)	401 (100)	15 (100)	.29
Male	2 (0.3)	2 (0.9)	0	0	0	
Race/ethnicity						
White, non-Hispanic	422 (63.5)	155 (67.1)	9 (50)	249 (62.1)	9 (60)	.67
Black, non-Hispanic	93 (14)	25 (10.8)	5 (27.8)	61 (15.2)	2 (13.3)	
Hispanic	103 (15.5)	37 (16)	3 (16.7)	60 (15)	3 (20)	
Other ^a	47 (7.1)	14 (6.1)	1 (5.6)	31 (7.7)	1 (6.7)	
Histology/subtype						
DCIS	101 (15.2)	45 (19.5)	2 (11.1)	53 (13.2)	1 (6.7)	.12
Invasive HR +	478 (71.9)	166 (71.9)	13 (72.2)	289 (72.1)	10 (66.7)	
Invasive HER2 +	19 (2.9)	5 (2.2)	1 (5.6)	13 (3.2)	0	
Invasive TN	67 (10.1)	15 (6.5)	2 (11.1)	46 (11.5)	4 (26.7)	
Pathologic T stage						
T0	39 (5.9)	11 (4.8)	0	24 (6)	4 (26.7)	.006
Tis	109 (16.4)	48 (20.8)	2 (11.1)	58 (14.5)	1 (6.7)	
T1mic	15 (2.3)	1 (0.4)	0	13 (3.2)	1 (6.7)	
T1a	64 (9.6)	20 (8.7)	2 (11.1)	42 (10.5)	0	
T1b	127 (19.1)	47 (20.3)	0	76 (19)	4 (26.7)	
T1c	196 (29.5)	72 (31.2)	8 (44.4)	115 (28.7)	1 (6.7)	
T2	113 (17)	31 (13.4)	6 (33.3)	72 (18)	4 (26.7)	
T3	2 (0.3)	1 (0.4)	0	1 (0.2)	0	
Pathologic N stage						
N0	561 (84.3)	204 (88.3)	16 (88.9)	327 (81.5)	14 (93.3)	.13
N0(i +)	25 (3.8)	5 (2.2)	1 (5.6)	19 (4.7)	0	
N1a	26 (3.9)	4 (1.7)	0	22 (5.5)	0	
N1mic	27 (4.1)	6 (2.6)	0	20 (5)	1 (6.7)	
Nx	26 (3.9)	12 (5.2)	1 (5.6)	13 (3.2)	0	
Histologic grade						
Low	156 (23.5)	48 (20.8)	8 (44.4)	137 (34.2)	11 (73.3)	<.001
Moderate	301 (45.3)	65 (28.1)	1 (5.6)	88 (21.9)	2 (13.3)	
High	204 (30.7)	117 (50.6)	9 (50)	173 (43.1)	2 (13.3)	
Unknown	4 (0.6)	1 (0.4)	0	3 (0.7)	0	

(continued on next page)

Table 1 (Continued)

Characteristic	Total, n (%)	UK-FAST FORWARD, n (%)	UK-FAST, n (%)	Canadian/ START-B, n (%)	Conventional, n (%)	P value
Treatment site						
Whole breast	597 (89.8)	219 (94.8)	18 (100)	346 (86.3)	14 (93.3)	.003
Whole breast + axilla	68 (10.2)	12 (5.2)	0	55 (13.7)	1 (6.7)	
Type of chemotherapy						
None	493 (74.1)	190 (82.3)	14 (77.8)	283 (70.6)	6 (40)	<.001
Neoadjuvant	74 (11.1)	19 (8.2)	3 (16.7)	51 (12.7)	1 (6.7)	
Adjuvant	98 (14.7)	22 (9.5)	1 (5.6)	67 (16.7)	8 (53.3)	
Radiation start period						
2020, Mar-Apr	46 (6.9)	1 (0.4)	1 (5.6)	41 (10.2)	3 (20)	.002
2020, May-Jun	95 (14.3)	35 (15.2)	1 (5.6)	57 (14.2)	2 (13.3)	
2020, Jul-Aug	99 (14.9)	42 (18.2)	3 (16.7)	51 (12.7)	3 (20)	
2020, Sept-Oct	97 (14.6)	35 (15.2)	7 (38.9)	55 (13.7)	0	
2020, Nov-Dec	110 (16.5)	45 (19.5)	3 (16.7)	58 (14.5)	4 (26.7)	
2021, Jan-Feb	70 (10.5)	23 (10)	3 (16.7)	44 (11)	0	
2021, Mar-Apr	109 (16.4)	37 (16)	0	71 (17.7)	1 (6.7)	
2021, May	39 (5.9)	13 (5.6)	0	24 (6)	2 (13.3)	
Tumor bed boost						
No	238 (35.8)	129 (55.8)	7 (38.9)	100 (24.9)	2 (13.3)	<.001
Yes	427 (64.2)	102 (44.2)	11 (61.1)	301 (75.1)	13 (86.7)	
Distance to hospital, miles						
<25	288 (43.3)	80 (34.6)	7 (38.9)	192 (47.9)	9 (60)	.005
25-49	122 (18.3)	41 (17.7)	4 (22.2)	76 (19)	1 (6.7)	
50-149	113 (17)	46 (19.9)	4 (22.2)	61 (15.2)	2 (13.3)	
150-499	104 (15.6)	54 (23.4)	2 (11.1)	48 (12)	0	
500-5000	28 (4.2)	8 (3.5)	1 (5.6)	17 (4.2)	2 (13.3)	
International	10 (1.5)	2 (0.9)	0	7 (1.7)	1 (6.7)	
Insurance						
Managed care	419 (63)	114 (49.4)	10 (55.6)	284 (70.8)	11 (73.3)	<.001
Medicare	218 (32.8)	110 (47.6)	8 (44.4)	98 (24.4)	2 (13.3)	
Government/military	3 (0.5)	2 (0.9)	0	0	1 (6.7)	
Medicaid	7 (1.1)	1 (0.4)	0	5 (1.2)	1 (6.7)	
Self-pay	11 (1.7)	2 (0.9)	0	9 (2.2)	0	
Other	7 (1.1)	2 (0.9)	0	5 (1.2)	0	

Abbreviations: DCIS = ductal carcinoma in situ; HR = hormone receptor; TN = triple-negative.
 Bold values indicate statistically significant associations at P<0.05.
^a Other refers to Asian and Native American race.

year of medical school graduation, annual volume of patients with breast cancer, academic rank, and site of practice, that were significantly associated with use of ultra-HF-WBI.

Discussion

This study describes the patterns of ultra-HF-WBI adoption at 1 large academic institution from March 2020

Table 2 Treating physician characteristics (N = 21)

Physician characteristics	Total, n (%)
Attending sex	
Female	13 (61.9)
Male	8 (38.1)
Attending race	
White, non-Hispanic	12 (57.1)
Black, non-Hispanic	3 (14.3)
Asian, non-Hispanic	3 (14.3)
Hispanic, any race	2 (9.5)
American Indian or Alaska Native, non-Hispanic	1 (4.8)
Attending year of medical school graduation	
1982-1999	6 (28.6)
2000-2004	6 (28.6)
2005-2009	5 (23.8)
2010-2015	4 (19)
Attending annual volume of patients with breast cancer	
≤40	3 (14.3)
41-100	12 (57.1)
>100	6 (28.6)
Attending academic rank	
Assistant professor	5 (23.8)
Associate professor	8 (38.1)
Professor	8 (38.1)
Attending involvement with residents	
No	11 (52.4)
Yes	10 (47.6)
Number of anatomic disease sites treated	
1	11 (52.4)
>1	10 (47.6)
Attending practice location	
Main hospital campus	10 (47.6)
Regional campus	11 (52.4)

to May 2021. There was increased adoption of this approach, in particular the UK-FF dose fractionation, throughout the study's period. The largest increase occurred from March-April 2020 to May-June 2020, indicating that practice changed as a response to published data in combination with the COVID-19 pandemic. Additionally, factors indicative of lower risk cancer diagnoses, including older age, low histologic grade, receipt of WBI without inclusion of the low axilla, and omission of boost radiation, were associated with use of ultra-HF-WBI, suggesting that physicians considered disease-related factors and UK-F/UK-FF trial eligibility criteria in their fractionation decision.^{3,4} Moreover, patients with

farther travel distance from the treating hospital were more likely to receive ultra-HF-WBI, suggesting that fractionation decisions were also patient-centered; use of short fractionation schemes was likely selected to help reduce patient travel and lodging costs during a course of radiation therapy. Finally, compared with previous studies,^{13,14} physician-level variation was substantial, accounting for 21.7% of variation in the outcome.

The implementation of published research into clinical practice can take years, with limited data exploring this phenomenon related to adoption of ultrahypofractionation for breast cancer. After the UK-FF primary publication in April 2020,⁴ the use of UK-F and UK-FF regimens

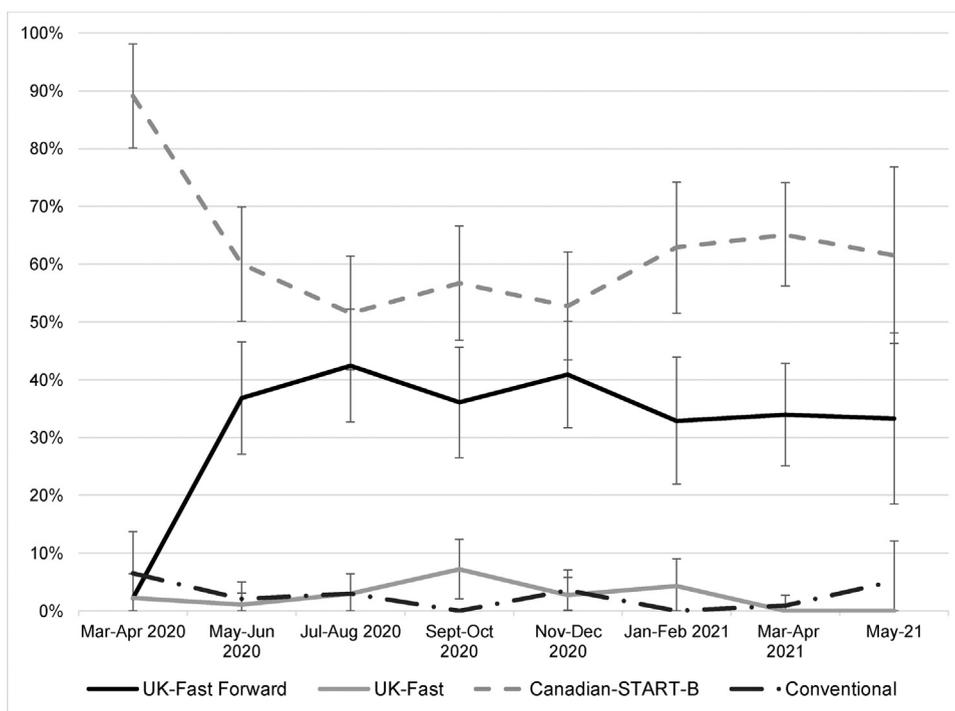


Fig. 1 Percentage of patients requiring whole-breast radiation therapy from March 2020 to May 2021 stratified by the type of fractionation prescribed.

increased substantially at our institution. This period coincided with the first wave of the COVID-19 pandemic in our community, which was likely a significant contributor to the greater use of ultra-HF-WBI owing to efforts to minimize patient time spent in the hospital during the early portion of the pandemic. However, other factors also may have contributed to the change in practice favoring ultra-HF-WBI. Jacobs et al analyzed the translation of research findings to clinical practice in 1 breast cancer radiation treatment center in Europe and found that “level of evidence” was the primary facilitator to the implementation of new research findings.¹⁵ The phase 3, randomized design and 5 years of follow-up data in the UK-FF primary publication served as a robust level of evidence and likely contributed to the increased use of UK-F and UK-FF at our institution. Another previous study found an increase in use of the Canadian and START-B treatment regimens in ESBC after publication of American Society for Radiation Oncology guidelines endorsing HF-WBI¹⁶; these guidelines have not yet been updated to reflect the results of UK-FF. However, the United Kingdom has updated their breast cancer guidelines to recommend using ultra-HF-WBI,¹⁷ suggesting international acceptance of ultra-HF-WBI. Despite variations in community-levels of COVID-19 spread as well as greater availability of personal protective equipment and other COVID-19-related precautions, our institution continues to use ultra-HF-WBI at a fairly stable rate. This suggests that although the pandemic may have expedited the initial

use of ultra-HF-WBI, the confidence in the UK-F and UK-FF clinical trial findings, specifically the 5-year follow-up data paralleling locoregional recurrence data from HF-WBI studies, continue to motivate our treating physicians to use these ultra-HF-WBI regimens in selected patients. It is important for the field of radiation oncology to be aware of the discrepancy between publication of trial results and implementation into clinical practice. To improve implementation of ultra-HF-WBI, future studies should identify the current gaps to implementation at the provider and the hospital level to facilitate tailored and effective interventions such as financial support, physician endorsement, communication about outcomes, and patient satisfaction with ultra-HF-WBI.^{18,19}

We identified several patient factors that were associated with use of ultra-HF-WBI. Patients with low-risk disease, as signified by low histologic grade, older age, and no requirement for either low axilla radiation or a tumor bed boost, were more likely to receive UK-F or UK-FF. This suggests that physicians considered disease-related factors in making their treatment decisions. Patients with a lower risk of relapse, especially those of older age who are less likely to have consequences of late effects, may provide reassurance for treating physicians in using newer ultra-HF-WBI regimens that have less follow-up data than HF-WBI or CF-WBI compared with treating patients with a higher relapse risk. Alternatively, lack of ultra-HF-WBI use in patients requiring radiation to their low axilla may reflect treating physicians’ hesitancy to implement

Table 3 Multivariable hierarchical logistic regression model for use of the UK-FAST or UK-FAST FORWARD radiation fractionation regimens

Patient characteristics	Multivariate model		
	Risk ratio*	95% CI	P value
Age, y			
18-49	1		
50-59	2.67	1.57-3.99	.001
60-69	4.06	2.76-5.25	<.001
70 and older	5.49	4.23-6.31	<.001
Race			
White, non-Hispanic	1		
Black, non-Hispanic	1.12	0.74-1.53	.57
Hispanic	1.39	1.01-1.75	.05
Other	1.44	0.89-1.94	.13
Histologic grade			
High	1		
Low	1.63	1.14-2.16	.01
Moderate	1.49	1.08-1.94	.02
Unknown	0.61	0.04-2.85	.66
Treatment site			
Whole breast + axilla	1		
Whole breast only	2.65	1.62-3.73	.004
Radiation start			
2020, Mar-Apr	1		
2020, May-Jun	12.44	3.66-20.09	<.001
2020, Jul-Aug	14.91	5.26-20.99	<.001
2020, Sept-Oct	13.22	4.12-20.39	<.001
2020, Nov-Dec	13.78	4.48-20.6	<.001
2021, Jan-Feb	11.76	3.25-19.85	.001
2021, Mar-Apr	11.84	3.36-19.82	.001
2021, May	9.97	2.28-19.23	.005
Boost			
Yes	1		
No	1.97	1.55-2.38	<.001
Distance to hospital, miles			
<25	1		
25-49	1.03	0.66-1.49	.89
50-149	1.51	1.05-1.99	.03
≥150 or international	1.92	1.45-2.35	<.001

Abbreviations: CI = confidence interval; DCIS = ductal carcinoma in situ; HR = hormone receptor; TN = triple-negative.
 Bold values indicate statistically significant associations at $P < 0.05$.
 * Odds ratios were converted to risk ratios per the method described by Zhang and Yu.¹¹

radiation approaches that were not explicitly studied in the clinical trial. Although travel distance was a significant factor predisposing patients to use of ultra-HF-WBI, it remains important to note that ultra-HF-WBI may also

be offered to patients who live close to the treating hospital as well to help decrease treatment time and expense and free up patient time for work, caregiving roles, and leisure.

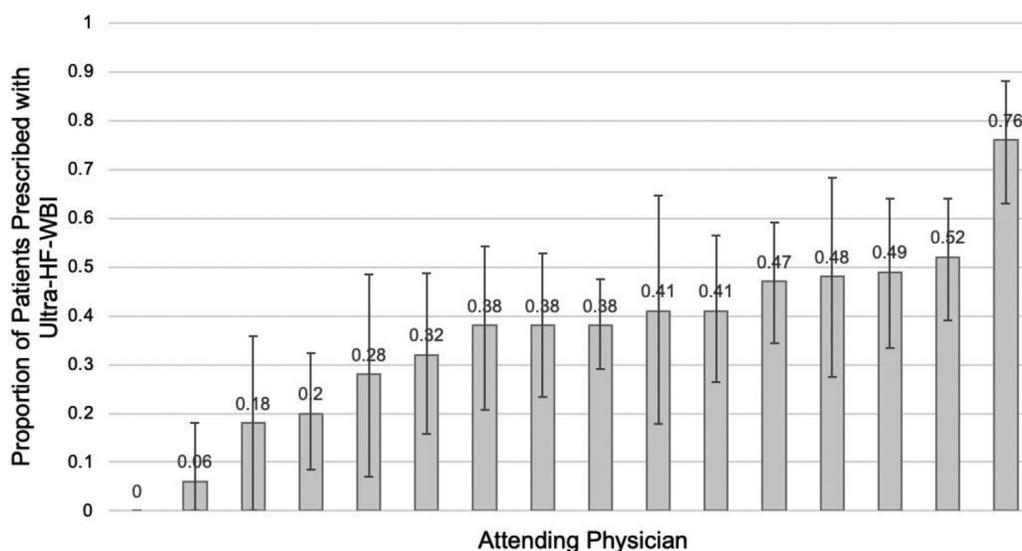


Fig. 2 Proportion of patients receiving the UK-FAST or UK-FAST FORWARD fractionation regimen stratified by each treating physician. Sixteen attending physicians who treated at least 10 patients with breast cancer were included in this analysis. The 95% confidence interval bars take into account variability of the calculated rate based on the number of patients treated by each physician. *Abbreviation:* ultra-HF-WBI = ultrahypofractionated whole-breast irradiation.

In addition to increased use of ultra-HF-WBI during the past year, our institution also uses HF-WBI, such as the Canadian and START-B regimens, at high rates. Conventionally fractionated WBI was used in only 2% of patients with DCIS or ESBC, suggesting that our institution has nearly completely adopted hypofractionation for DCIS and ESBC. A limited number of studies have evaluated the adoption of HF-WBI in the United States after publication of primary trial results. The available studies have shown overall low rates of HF-WBI use^{20,21} until the publication of long-term (>10 years) follow-up data, establishment of multidisciplinary tumor board discussions, or cancer society endorsement of HF-WBI regimens.^{16,22} To prevent a similarly slow implementation of ultra-HF-WBI regimens, it may be helpful for other institutions to publish their experience with ultra-HF-WBI to increase confidence and initiate discussions across the country. Overall, regular discussions among cancer societies and oncologists, and with patients, about new radiation regimens with timely recommendations about such regimens may help with informed and patient-centered decision-making.²³

In this study, no factors related to the treating physicians were associated with increased use of ultra-HF-WBI. This may be due to our centralized quality assurance review of each patient that is performed weekly and is inclusive of all practice sites. In contrast, after the publication of the Canadian/START-B HF-WBI trials, studies demonstrated that there was initially greater use of the HF-WBI regimens at main hospital centers and centers with a greater density of radiation oncologists.^{7,24} In a field driven by data and clinical trials, we need to ensure

continued flow of information and dialogue within and between all treating centers, including large academic hospitals, regional clinics, and nonacademic rural clinics. Additionally, Boero et al found that the individual radiation oncologist had the greatest effect on use of Canadian/START-B regimens in Medicare patients after these trials were published, with this trend continuing through time despite additional publications of long-term follow-up data.²⁵ Our study showed a wide gap among our treating physicians in the proportion of ultra-HF-WBI use (0% to 75%). There are variations in referral of ESBC patients to these physicians from medical and surgical oncology; however, standards do not exist for evaluating the quality of new evidence and guiding practice-changing decision-making in our field. More effort should be made to establish criteria for when new trial findings should prompt changes in standard-of-care clinical practice so that the health care environment and the treating physician are not primary influencers for the care that a patient receives.

Physician compensation is 1 important factor not addressed in this study that may have an effect on adoption of ultra-HF-WBI. Radiation oncologist compensation varies throughout the country depending on the site of employment and use of fee-for-service models. At our institution, physicians are not compensated based on the radiation regimen prescribed or work-relative value units; thus, there is no difference in compensation between physicians who prescribe CF-WBI versus ultra-HF-WBI, despite known differences in revenue generated. This flexibility may have facilitated the prompt adoption of ultra-HF-WBI after the primary UK-FF publication. Physicians who are

compensated based on per-patient revenue may experience decreased compensation per patient when prescribing ultra-HF-WBI, because fee-for-service models incentivize delivery of more fractions.²⁶ However, ultra-HF-WBI increases capacity and facilitates the treatment of more patients, which will increase compensation when demand is high. Nevertheless, we suspect that fee-for-service financial models serve as a barrier to implementation of ultra-HF-WBI in patients with DCIS or ESBC.

Our study has limitations. We aimed to describe the patterns of hypofractionation at our institution during the past year and potential factors associated with these patterns; however, it is not possible to determine whether the primary factor in the adoption of UK-FF was the high-quality evidence published in the primary trial publication or the COVID-19 pandemic. Moreover, our analysis described hypofractionation trends from a single institution with a unique compensation model, which limits the generalizability of our findings. Further studies are needed to investigate hypofractionation trends and identify barriers to the implementation of hypofractionation at other institutions. Additionally, our analysis lacks information about central axis separation or qualitative data, which may have provided additional factors that played a role in the adoption of ultra-HF-WBI at our institution. Finally, we excluded patients who were treated with PBI, because a majority of these patients are treated on active investigator-initiated clinical trials with specified PBI dose-fractionation. Despite these limitations, our study demonstrated a clear adoption of ultra-HF-WBI among a robust sample size and diverse group of treating physicians and should be considered in future discussions about use of ultra-HF-WBI regimens.

Conclusion

Our institution adopted the UK-F and UK-FF ultra-HF-WBI radiation treatment regimens for DCIS and ESBC immediately after publication of randomized evidence supporting its use in more than one-third of eligible patients. The COVID-19 pandemic likely played a role in the rapid adoption of ultra-HF-WBI; however, several other factors were also associated with use of ultra-HF-WBI. Ultra-HF-WBI was preferentially used in patients with lower-risk disease and in patients who traveled a farther distance for treatments, suggesting careful, patient-centered selection for this new approach. One year after the UK-FF trial publication, our institution continues to use ultra-HF-WBI at high rates despite fluctuations in the pandemic. These findings support thoughtful implementation of new, evidence-based radiation regimens to

facilitate more standard practice patterns across sites and physicians.

References

- Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med*. 2010;362:513–520.
- 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*. 2013;14:1086–1094.
- Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. *J Clin Oncol*. 2020;38:3261–3272.
- Brunt AM, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multi-centre, non-inferiority, randomised, phase 3 trial. *Lancet*. 2020;395:1613–1626.
- Taylor TN, Kinchen CL, Johnstone CA, Robbins JR. Practice patterns in radiation therapy for bone metastases in multiple histologies. *J Clin Oncol*. 2017;35(31suppl):151.
- Batumalai V, Delaney GP, Descallar J, et al. Variation in the use of radiotherapy fractionation for breast cancer: Survival outcome and cost implications. *Radiother Oncol*. 2020;152:70–77.
- Bekelman JE, Sylwestrzak G, Barron J, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008–2013. *JAMA*. 2014;312:2542–2550.
- McCormick B, Ottesen RA, Hughes ME, et al. Impact of guideline changes on use or omission of radiation in the elderly with early breast cancer: Practice patterns at National Comprehensive Cancer Network institutions. *J Am Coll Surg*. 2014;219:796–802.
- Hait WN. Translating research into clinical practice: Deliberations from the American Association for Cancer Research. *Clin Cancer Res*. 2005;11:4275–4277.
- Recht A. Hypofractionated whole-breast irradiation: Case closed? *J Clin Oncol*. 2020;38:3584–3586.
- Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. 1998;280:1690–1691.
- Austin PC, Merlo J. Intermediate and advanced topics in multilevel logistic regression analysis. *Stat Med*. 2017;36:3257–3277.
- Hoffman KE, Niu J, Shen Y, et al. Physician variation in management of low-risk prostate cancer: A population-based cohort study. *JAMA Intern Med*. 2014;174:1450–1459.
- Eberth JM, Xu Y, Smith GL, et al. Surgeon influence on use of needle biopsy in patients with breast cancer: A national medicare study. *J Clin Oncol*. 2014;32:2206–2216.
- Jacobs M, Boersma L, Merode FV, et al. How efficient is translational research in radiation oncology? The example of a large Dutch academic radiation oncology department. *Br J Radiol*. 2016;89:20160129.
- Badiyan SN, Shah C, Arthur D, et al. Hypofractionated regional nodal irradiation for breast cancer: Examining the data and potential for future studies. *Radiother Oncol*. 2014;110:39–44.
- Coles CE, Aristei C, Bliss J. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. *Clin Oncol (R Coll Radiol)*. 2020;32:279–281.
- Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. *BMC Psychol*. 2015;3:32.

19. Adesoye T, Greenberg CC, Neuman HB. Optimizing cancer care delivery through implementation science. *Front Oncol.* 2016;6:1.
20. Jagsi R, Falchook AD, Hendrix LH, Curry H, Chen RC. Adoption of hypofractionated radiation therapy for breast cancer after publication of randomized trials. *Int J Radiat Oncol Biol Phys.* 2014;90:1001–1009.
21. Wang EH, Mougalian SS, Soulos PR, et al. Adoption of hypofractionated whole-breast irradiation for early-stage breast cancer: A National Cancer Data Base analysis. *Int J Radiat Oncol Biol Phys.* 2014;90:993–1000.
22. Garda AE, Shaffer LE, Gokhale AS, et al. Adoption of hypofractionated radiation therapy for early stage breast cancer in a community based radiation oncology practice. *Int J Radiat Oncol Biol Phys.* 2017;99:E16–E17.
23. Gillespie EF, Khan AJ, Cahlon O, Braunstein LZ. Are 5-year randomized clinical trial results sufficient for implementation of short-course whole breast radiation therapy? *Pract Radiat Oncol.* 2021;11:301–304.
24. Gillespie EF, Matsuno RK, Xu B, et al. Geographic disparity in the use of hypofractionated radiation therapy among elderly women undergoing breast conservation for invasive breast cancer. *Int J Radiat Oncol Biol Phys.* 2016;96:251–258.
25. Boero IJ, Gillespie EF, Hou J, et al. The impact of radiation oncologists on the early adoption of hypofractionated radiation therapy for early-stage breast cancer. *Int J Radiat Oncol Biol Phys.* 2017;97:571–580.
26. Konski A, Yu JB, Freedman G, Harrison LB, Johnstone PA. Radiation oncology practice: Adjusting to a new reimbursement model. *J Oncol Pract.* 2016;12:e576–e583.