Original Investigation

Differences in the Acute Toxic Effects of Breast Radiotherapy by Fractionation Schedule
Comparative Analysis of Physician-Assessed and Patient-Reported Outcomes in a Large Multicenter Cohort

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IMPORTANCE Randomized trials have established the long-term safety and efficacy of hypofractionated whole-breast radiotherapy, but little is known about the acute toxic effects experienced by patients treated with hypofractionation as compared with conventional fractionation, particularly in real-world settings and from the patient's own perspective.

OBJECTIVE To evaluate prospectively collected data on acute toxic effects and patient-reported outcomes in a cohort treated with varying radiation fractionation schemes in practices collaborating in the Michigan Radiation Oncology Quality Consortium (MROQC).

DESIGN, SETTING, AND PARTICIPANTS We compared toxic effects in patients receiving hypofractionation (HF) vs conventional fractionation (CF) during treatment (through 7 days after treatment) and in follow-up (posttreatment days 8-210), after adjustment for sociodemographic, clinical, and treatment characteristics. The MROQC includes academic and community radiation oncology practices across Michigan. All 2604 patients who received adjuvant whole-breast radiotherapy after lumpectomy for unilateral breast cancer at MROQC participating sites from October 2011 through June 2014 were registered; we analyzed 2309 for whom there was a comprehensive physician toxicity evaluation within 1 week of completion of radiotherapy and at least 1 weekly toxicity evaluation during treatment.

EXPOSURES Hypofractionation vs CF.

MAIN OUTCOMES AND MEASURES Physicians reported dermatitis, pain, fatigue, and other common toxic effects associated with breast radiotherapy at baseline, weekly during radiotherapy, and in follow-up. Patients who consented also rated their own experiences, including breast pain, fatigue, and being bothered by symptoms.

RESULTS Of the 2309 evaluable patients, 578 received HF. During treatment, after adjustment for sociodemographic, clinical, and treatment factors, patients receiving CF had significantly higher maximum physician-assessed skin reaction (moist desquamation, 28.5% vs 6.6%, $P < .001$; grade ≥2 dermatitis, 62.6% vs 27.4%, $P < .001$), self-reported pain (moderate/severe pain, 41.1% vs 24.2%, $P = .003$), burning/stinging bother (often/always, 38.7% vs 15.7%, $P = .002$), hurting bother (33.5% vs 16.0%, $P = .001$), swelling bother (29.6% vs 15.7%, $P = .03$), and fatigue (29.7% vs 18.9%, $P = .02$) but slightly greater absence of skin induration in follow-up (84.5% vs 81.2%, $P = .02$). No significant differences were observed in any other measured outcomes during follow-up extending through 6 months.

CONCLUSIONS AND RELEVANCE Hypofractionation not only improves convenience but also may reduce acute pain, fatigue, and the extent to which patients are bothered by dermatitis in patients with breast cancer undergoing whole-breast radiotherapy.

JAMA Oncol. 2015;1(7):918-930. doi:10.1001/jamaoncol.2015.2590
Published online August 6, 2015.

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Randomized trials have established that hypofractionated regimens of radiotherapy to the whole breast can provide long-term disease control that is equivalent to the excellent outcomes of more protracted conventional fractionation schedules in selected patients undergoing lumpectomy for breast cancer.[1,2] Hypofractionation might also result in lower rates of late toxic effects than conventional fractionation.[2] Although the American Society for Radiation Oncology has issued consensus guidelines[3] to identify patients in whom hypofractionation is appropriate and endorsed consideration of hypofractionation in its Choosing Wisely campaign,[4] uptake of hypofractionated regimens has demonstrated considerable variability worldwide[5-8] and has been relatively slow within the United States.[9-11]

The hypofractionated schedules evaluated in recent trials have deliberately paired the increase in fraction size with lower total dose, given concerns about toxicity when large fraction sizes were used to deliver higher total doses to the whole breast.[12] Scholars have suggested that breast cancer cells may have a lower α to β ratio than typically ascribed to tumor cells, which renders them vulnerable to larger dose per fraction and allows for tumor control at lower total doses than when dose per fraction is smaller. Because acute-reacting normal tissues are expected to demonstrate toxic effects that relate to total dose, with lesser dependence on fraction size, it is possible that the use of schedules such as 42.5 Gy in 16 fractions or 40 Gy in 15 fractions might actually result in lower rates of bothersome symptoms that typically occur during and soon after radiation treatment, including dermatitis, pain, and fatigue, with important implications for quality of life. However, the reports of randomized trials to date have provided little information comparing acute toxic effects with hypofractionation as compared with conventional fractionation,[13-17] and no evidence of comparative effectiveness or patient-reported outcomes has been available from cohorts of patients treated outside the context of clinical trials.

The Michigan Radiation Oncology Quality Consortium (MROQC) is a multicenter, prospective collaboration through which detailed clinical, sociodemographic, treatment, dosimetric, and outcomes data are collected for patients receiving adjuvant radiotherapy after lumpectomy at 18 centers in the state of Michigan.[10] It is funded by Blue Cross Blue Shield of Michigan, but data are collected on all eligible patients within participating practices, regardless of insurance type. Because MROQC includes physician-assessed and patient-reported toxicity information from a large cohort of patients treated with varying fractionation schedules outside the context of selective and controlled clinical trials settings, it provides a unique opportunity to document in detail the acute toxic effects experienced by patients receiving breast radiotherapy in modern practice. It also allows for an evaluation of the comparative effectiveness of hypofractionated regimens as compared with conventional fractionation schedules in terms of the frequency and severity of acute toxic effects that commonly occur during adjuvant whole-breast radiotherapy.

At a Glance

- Our consortium evaluated the acute toxic effects experienced by patients treated with hypofractionated whole-breast radiotherapy as compared with conventional fractionation using both physician-assessed and patient-reported outcome measures.
- During treatment, patients receiving conventionally fractionated whole-breast radiotherapy had significantly higher maximum physician-assessed skin reaction (grade ≥2 dermatitis, 62.6% vs 27.4%; $P < .001$).
- Patients treated with conventional fractionation also had higher rates of self-reported breast pain than those treated with hypofractionation (moderate/severe pain, 41.1% vs 24.2%; $P = .003$).
- Hypofractionation not only improves convenience but is also associated with less acute pain, fatigue, and dermatitis among patients with breast cancer.

Methods

Sample

We considered a cohort of patients with breast cancer registered by MROQC (an institutional review board–approved initiative with consent waiver) from its inception in October 2011 through June 2014. From the 2604 patients identified as receiving adjuvant radiotherapy after lumpectomy for unilateral breast cancer during that selection period, we limited the cohort to the 2318 for whom there was a comprehensive physician toxicity evaluation within 1 week of completion of radiotherapy (which we defined as the "end of treatment evaluation"), as well as at least 1 weekly toxicity evaluation during treatment. We further excluded 9 patients registered by newly participating institutions that had not yet registered more than 10 patients, in order to allow for quality control and analysis by institution. This left 2309 patients in the final sample for analysis of physician-evaluated outcomes during treatment. Follow-up physician assessments, completed at visits between 8 and 210 days after end of treatment, were available for 1781 of the 2309 patients.

Of the 2309 patients analyzed for physician-assessed outcomes during treatment, 1723 patients had completed at least the comprehensive end-of-treatment questionnaire and at least 1 weekly questionnaire during treatment; these 1723 women constituted the sample for analysis of patient-reported outcomes. Follow-up patient questionnaires, completed between 8 and 210 days after end of treatment, were available for 1368 of these 1723 patients.

Measures

Physicians were asked to complete toxicity forms at baseline, weekly during treatment, and approximately 3 months after treatment, as well as during any other follow-up visits. These physician toxicity forms (eAppendix 1 in the Supplement) included lists of Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, toxicities commonly observed

during and after treatment. Weekly treatment forms evaluated breast pain, chest wall pain, radiation dermatitis, lymphedema, and fatigue on the CTCAE grading scale (with definitions provided). Physicians were also asked whether the patient had moist desquamation and whether she had dry desquamation. Forms for physician assessments at end of treatment and in follow-up included all of these items, as well as CTCAE grading for pruritus, skin induration, dyspnea, pleuritic pain, pneumonitis, pericarditis, and pericardial effusion.

Patients who consented to participate in patient-reported outcomes collection were also given detailed questionnaires at these same time points (eAppendix 2 in the Supplement). The questionnaires were developed using standard techniques for survey design,[18] including incorporation of existing validated instruments where possible and evaluation using detailed cognitive pretesting.[19] The weekly treatment forms included ratings of pain from a 4-item modified Brief Pain Inventory[20] (modified to specify breast pain), radiation skin reaction (using items developed specifically for this purpose), and bother related to the acute radiation reaction as assessed through an 8-item modified Skindex questionnaire[21] (specifying bother related to the radiation reaction rather than the more general "skin condition" terminology in the original instrument). The end-of-treatment forms included these items and items evaluating fatigue, satisfaction with treatment, and impact of radiotherapy adverse effects (using items developed in previous work by our research group). Follow-up questionnaires included the same measures of pain, skin reaction, and bother related to radiation reaction, as well as the detailed Breast Cancer Treatment Outcomes Scale.[22] Of note, patient-reported information collected on these questionnaires was used for classification of patient race in this study, using options provided by the investigators. Where patient-reported information on race was missing, race was classified into these investigator-defined categories based on review of medical records. Race was included as a covariate because the primary acute toxic effect of breast radiotherapy is dermatitis, which might manifest differently or be measured in systematically different ways by race (eg, because erythema is more difficult to appreciate in darker skin types).

Dosimetric information was collected through medical physics data forms completed by dosimetrists at each participating site, as well as composite dose-volume histograms and DICOM (Digital Imaging and Communications in Medicine)–formatted files of the actual treatment plans that were uploaded to MROQC for each patient. These sources provided the information regarding fractionation schedule (which we considered, as in our previous work, to be hypofractionated if at least some radiotherapy fractions to the whole breast were >2 Gy in size—95% of these were 2.6-2.7 Gy; patients for whom all radiotherapy fractions to the whole-breast field were ≤2 Gy were considered to have received conventional fractionation—62.9% of these were 1.8 Gy and 37.1% were 2.0 Gy), whether nodes were treated, mean breast dose, maximum dose to 1 cm^3 of breast volume, and whether a boost was delivered.

Analysis

Two outcome measures were designated as co-primary end points for toxicity analyses a priori: patient-reported breast pain and physician-assessed moist desquamation. We first described the sample, stratified by fractionation schedule, for a number of key sociodemographic, clinical, and treatment factors: age, race, diabetes mellitus, hypertension, breast volume, separation distance from breast tangent entry to exit (which affects the ability to achieve homogeneous dose), body mass index, T stage, laterality, chemotherapy use, hormone therapy use, whether nodes were treated, mean breast dose, maximum dose to 1 cm^3 of breast volume, and whether a boost was delivered. We then evaluated the maximum toxicity rating reported during treatment through 7 days after treatment, as well as during a 6-month follow-up period (8-210 days after treatment), for each physician-assessed and patient-reported toxic effect in turn. We compared each toxicity outcome between patients receiving conventional fractionation and hypofractionation after adjustment for the same set of potentially confounding sociodemographic, clinical, and treatment factors, using either a mixed-effects cumulative logit or mixed-effects logistic model depending on the levels of the outcome evaluated. The mixed-effects extension to standard linear models allows for the creation of hierarchical linear models in which the effects at the patient level can be nested within institution, and in which the independent effect of any given institution is not of interest, but rather, of interest is the generalization to the population of all possible institutions.[23-25] In this article, potentially confounding covariates at the patient level were modeled as fixed effects whereas institution was modeled as a random effect. $P \leq .05$ was considered statistically meaningful.

Finally, we conducted a sensitivity analysis within a more homogeneous subgroup of the overall study sample to evaluate consistency with findings in the larger cohort. Specifically, we evaluated the distribution of the 2 co-primary end points (patient-assessed breast pain and physician-assessed moist desquamation) within the subgroup of patients who did not undergo regional nodal irradiation and who did receive boost treatment, and we constructed models as described in the Methods section within this smaller subgroup.

Results

Table 1 presents the characteristics of the 2309 patients in the study cohort, all of whom underwent lumpectomy and adjuvant radiotherapy to the whole breast and were registered in MROQC from October 2011 through June 2014. Of these patients, 578 received hypofractionated whole-breast radiotherapy, of whom 347 (60%) received boost, and 1731 received conventionally fractionated whole-breast radiotherapy, of whom 1608 (93%) received boost. As shown in Table 1, patients who received hypofractionation were older and of somewhat smaller body habitus, with smaller tumors and less frequency of nodal involvement, nodal radiation treatment, and chemotherapy receipt.

Table 1. Sample Description Stratified by Fractionation Schedule

Characteristic	Total Population (n = 2309)	Conventional Fractionation (n = 1731)	Hypofractionation (n = 578)	*P* Value
Age, y				
Mean (SD)	61.2 (11.1)	59.8 (10.8)	65.5 (11.0)	
No. (%)				
≤50	403 (17.5)	349 (20.2)	54 (9.3)	<.001
51-60	659 (28.6)	535 (30.9)	126 (21.8)	
61-70	743 (32.2)	556 (32.1)	188 (32.5)	
>70	501 (21.7)	291 (16.8)	210 (36.3)	
Race				
White	1697 (73.6)	1253 (72.4)	445 (77.0)	.04
Black	431 (18.7)	343 (19.8)	91 (15.7)	
Other	171 (7.4)	131 (7.6)	39 (6.8)	
Not reported	6 (0.3)	4 (0.2)	3 (0.5)	
Separation distance, mean (SD), cm	22.7 (3.9)	23.0 (4.0)	21.9 (3.3)	<.001[a]
Breast volume, mean (SD), cm^3	1197 (693)	1270 (729)	980 (513)	<.001[a]
BMI				
Mean (SD)	30.3 (7.1)	30.8 (7.4)	28.7 (6.1)	<.001
No. (%)				
≤25.0	574 (24.9)	410 (23.7)	164 (28.4)	
25.1-30.0	652 (28.2)	452 (26.1)	200 (34.6)	
30.1-35.0	530 (23.0)	410 (23.7)	120 (20.8)	
>35.0	506 (21.9)	428 (24.7)	78 (13.5)	
Not reported	47 (2.0)	31 (1.8)	16 (2.8)	
Diabetes mellitus, No. (%)	353 (15.3)	275 (15.9)	78 (13.5)	.16
Hypertension, No. (%)	1152 (49.9)	849 (49.1)	303 (52.4)	.16
T stage, No. (%)				
Tis	495 (21.4)	373 (21.6)	122 (21.1)	<.001
T0	8 (0.4)	7 (0.4)	1 (0.2)	
T1	1341 (58.1)	947 (54.8)	394 (68.1)	
T2	415 (18.0)	361 (20.9)	54 (9.3)	
T3/T4	29 (1.3)	25 (1.4)	4 (0.7)	
Not reported	21 (0.9)	18 (1.0)	3 (0.5)	
N stage, No. (%)				
NX	375 (16.2)	267 (15.4)	108 (18.6)	<.001
N0	1539 (66.7)	1101 (63.7)	438 (75.8)	
N1	301 (13.0)	274 (15.8)	27 (4.7)	
N2/N3	69 (3.0)	68 (3.9)	1 (0.2)	
Not reported	25 (1.1)	21 (1.2)	4 (0.7)	
Laterality, No. (%)				
Left breast	1179 (51.1)	894 (51.7)	285 (49.3)	.37
Right breast	1130 (48.9)	837 (48.4)	293 (50.7)	
Chemotherapy, No. (%)	700 (30.3)	627 (36.2)	73 (12.6)	<.001
Hormone therapy, No. (%)	1580 (68.4)	1189 (68.7)	391 (67.7)	.61
Nodes treated as part of plan, No. (%)	293 (12.7)	286 (16.5)	7 (1.2)	<.001

(continued)

Table 1. Sample Description Stratified by Fractionation Schedule (continued)

Characteristic	Total Population (n = 2309)	Conventional Fractionation (n = 1731)	Hypofractionation (n = 578)	*P* Value
Mean dose to the breast, Gy[b]				
Mean (SD)	50.4 (4.0)	52.1 (2.8)	45.3 (2.5)	
No. (%)				
≤48.0	578 (25.0)	95 (5.5)	483 (83.6)	<.001
48.1-51.0	590 (25.6)	522 (30.2)	68 (11.8)	
51.1-53.5	566 (24.5)	548 (31.7)	18 (3.1)	
>53.5	551 (23.9)	549 (31.7)	2 (0.4)	
Not reported	24 (1.0)	17 (1.0)	7 (1.2)	
Hot spot: maximum dose to 1 cm^3 of the breast, Gy[b]				
Mean (SD)	60.8 (6.5)	63.7 (3.7)	52.1 (5.3)	
No. (%)				
≤57.0	574 (24.9)	123 (7.1)	451 (78.0)	<.001
57.1-63.0	409 (17.7)	292 (16.9)	117 (20.2)	
63.1-65.0	733 (31.8)	731 (42.2)	2 (0.4)	
>65.0	569 (24.6)	568 (32.8)	1 (0.2)	
Not reported	24 (1.2)	17 (1.0)	7 (1.2)	
Boost delivered	1955 (84.7)	1608 (92.9)	347 (60.0)	<.001

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Wilcoxon rank-sum test, comparing medians.

[b] Metric taken from the composite dose-volume histogram.

Table 2 demonstrates the maximum physician-assessed toxic effects during treatment among patients treated with each fractionation approach. We observed substantial differences in physician-reported CTCAE scores for pain, dermatitis, and skin induration, found to be statistically significant even after adjustment for multiple confounding sociodemographic, clinical, and treatment factors as detailed in the Methods section and table footnote. Specifically, patients who received conventional fractionation were more likely to be rated as having moderate or severe (grade ≥2) breast pain (20.0% vs 5.9%; adjusted odds ratio [OR], 1.88 [95% CI, 1.24-2.84]; *P* = .003), at least grade 2 radiation dermatitis (62.6% vs 27.4%; adjusted OR, 2.42 [95% CI, 1.55-3.76]; *P* < .001), skin induration (21.1% vs 13.7%; adjusted OR, 1.98 [95% CI, 1.15-3.42]; *P* = .01), and chest wall pain (18.5% vs 6.8%; adjusted OR, 4.83 [95% CI, 2.54-9.20]; *P* < .001). Patients receiving conventional fractionation were more likely to have experienced moist desquamation (28.5% vs 6.6%; adjusted OR, 2.78 [95% CI, 1.54-5.03]; *P* < .001) and dry desquamation (58.8% vs 18.7%; adjusted OR, 2.83 [95% CI, 1.76-4.53]; *P* < .001) during treatment. Overall, patients receiving conventional fractionation were much more likely to experience at least 1 grade 2 or greater toxic effect during treatment than those treated with hypofractionation (67.7% vs 32.0%; adjusted OR, 2.24 [95% CI, 1.40-3.59]; *P* < .001).

Similar differences were observed for patient-reported outcomes. **Table 3** demonstrates the maximum patient-reported toxic effects during treatment, by fractionation approach, in the 1723 patients who consented and completed patient-reported outcomes questionnaires. Patients treated with conventional fractionation had increased maximum patient-reported pain, desquamation, fatigue, and bother related to burning/stinging, hurting, and swelling. Specifically, patients who received conventional fractionation were more likely to have reported moderate to severe breast pain (41.1% vs 24.2%; adjusted OR, 1.92 [95% CI, 1.25-2.96]; *P* = .003), moist desquamation (25.7% vs 3.8%; adjusted OR, 4.91 [95% CI, 2.35-10.28]; *P* < .001), dry desquamation (51.8% vs 12.2%; adjusted OR, 4.33 [95% CI, 2.49-7.53]; *P* < .001), frequent ("often" or "always") bother from burning or stinging of the skin of the treated breast (38.7% vs 15.7%; adjusted OR, 2.38 [95% CI, 1.39-4.06]; *P* = .002), frequent bother from the treated breast hurting (33.5% vs 16.0%; adjusted OR, 2.50 [95% CI, 1.44-4.33]; *P* = .001), frequent bother from swelling of the treated breast (29.6% vs 15.7%; adjusted OR, 1.88 [95% CI, 1.08-3.28]; *P* = .03), and significant fatigue (29.7% vs 18.9%; adjusted OR, 1.87 [95% CI, 1.11-3.15]; *P* = .02). No significant differences were observed for patient-reported satisfaction with radiation treatment with either fractionation approach.

In a sensitivity analysis conducted within a more homogenous subgroup of patients treated without regional nodal irradiation and with boost treatment, we observed qualitatively similar findings in the distribution of our co-primary end points. Specifically, among 1679 patients in this subgroup who were evaluable for physician-assessed toxic effects (1337 treated with conventional fractionation and 342 with hypofractionation), we observed rates of moist desquamation similar to those in the overall sample (27.8% among those treated with conventional fractionation and 8.2% among those treated with hypofractionation); this difference was not statistically significant (*P* = .06) in the multiple-variable models within this smaller subgroup. Among 1309 patients in this subgroup who were evaluable for patient-reported outcomes (1033 treated with conventional fractionation and 276 with hypofractionation), we observed similar rates of breast pain (29.2% moderate and

Table 2. Maximum Physician-Assessed Toxic Effects During Treatment Period

Toxic Effect	No. (%)		*P* Value[a]	Odds Ratio (95% CI)[a]
	Conventional Fractionation (n = 1731)	Hypofractionation (n = 578)		
Breast pain				
0	339 (19.6)	243 (42.0)	.003	1.88 (1.24-2.84)
1	1046 (60.4)	301 (52.1)		
2	320 (18.5)	31 (5.4)		
3	26 (1.5)	3 (0.5)		
Lymphedema of breast				
0	818 (47.3)	400 (69.0)	.09	1.44 (0.94-2.21)
1	804 (46.5)	171 (29.6)		
2	109 (6.3)	7 (1.2)		
Radiation dermatitis				
0	18 (1.0)	35 (6.0)	<.001	2.42 (1.55-3.76)
1	629 (36.4)	385 (66.6)		
2	1053 (60.8)	157 (27.2)		
3	31 (1.8)	1 (0.2)		
Pruritus				
0	1033 (59.8)	366 (63.3)	.53	0.87 (0.56-1.35)
1	685 (39.6)	202 (35.0)		
2	11 (0.6)	9 (1.6)		
3	0	1 (0.2)		
Missing	2	0		
Skin induration				
0	1364 (78.9)	499 (86.3)	.01	1.98 (1.15-3.42)
1	332 (19.2)	76 (13.2)		
2	32 (1.9)	3 (0.5)		
Missing	3	0		
Chest wall pain				
0	1412 (81.6)	539 (93.2)		
1	290 (16.8)	39 (6.8)		
2	27 (1.6)	0		
3	2 (0.1)	0		
1+	319 (18.5)	39 (6.8)	<.001	4.83 (2.54-9.20)
Pericarditis[b]				
0	1728 (99.9)	578 (100)		
1	2 (0.1)	0		
Missing	1	0		
Pericardial effusions[b]				
0	1728 (99.9)	578 (100)		
1	1 (0.1)	0		
Missing	2	0		
Dyspnea				
0	1683 (97.4)	569 (98.6)	.57	1.55 (0.35-6.84)
1	41 (2.4)	5 (0.9)		
2	4 (0.2)	3 (0.5)		
Missing	3	1		
Pleuritic pain[b]				
0	1723 (99.7)	576 (99.7)		
1	4 (0.2)	2 (0.4)		
2	1 (0.1)	0		
Missing	3	0		

(continued)

Table 2. Maximum Physician-Assessed Toxic Effects During Treatment Period (continued)

Toxic Effect	No. (%)		*P* Value[a]	Odds Ratio (95% CI)[a]
	Conventional Fractionation (n = 1731)	Hypofractionation (n = 578)		
Pneumonitis[b]				
0	1724 (99.7)	577 (99.8)		
1	2 (0.1)	1 (0.2)		
2	3 (0.2)	0		
Missing	2	0		
Fatigue				
0	234 (13.5)	165 (28.6)		
1	1288 (74.4)	390 (67.5)	.12	1.46 (0.91-2.35)
2	204 (11.8)	23 (4.0)		
3	5 (0.3)	0		
Maximum CTCAE-graded toxic effects (of those measured above)				
0	3 (0.2)	8 (1.4)		
1	557 (32.2)	385 (66.6)		
2	1115 (64.4)	181 (31.3)		
3	56 (3.2)	4 (0.7)		
2+	1171 (67.7)	185 (32.0)	<.001	2.24 (1.40-3.59)
Desquamation				
Moist				
Absent	1237 (71.5)	540 (93.7)	<.001	2.78 (1.54-5.03)
Present	493 (28.5)	38 (6.6)		
Dry				
Absent	714 (41.2)	470 (81.3)	<.001	2.83 (1.76-4.53)
Present	1017 (58.8)	108 (18.7)		

[a] Adjusted for breast volume, separation distance, body mass index, age, race, diabetes mellitus, hypertension, T stage, laterality, chemotherapy use, hormone therapy use, whether nodes were treated, mean breast dose, maximum dose to 1 cm^3 of breast volume, and whether a boost was delivered using either a cumulative logit or logistic model depending on the levels of the outcome.

[b] Not enough events to adjust for effects of covariates.

10.9% severe pain with conventional fractionation vs 23.9% moderate and 5.1% severe pain with hypofractionation); this difference remained statistically significant (P = .01) even in this smaller subgroup.

eTable 1 in the Supplement reports the maximum physician-assessed toxic effects observed from 8 to 210 days after treatment in the 1781 patients who had a physician follow-up visit and assessment during that period. We observed, as expected, low rates of maximal toxic effects during this period. There were no significant differences in maximum physician-assessed toxic effects reported during follow-up, except that patients treated with conventional fractionation were less likely to have skin induration (15.5% vs 18.8%; adjusted OR, 0.40 [95% CI, 0.19-0.85]; P = .02). Finally, eTable 2 in the Supplement presents the maximum patient-reported toxic effects during the posttreatment follow-up period; no significant differences were observed between patients receiving conventional fractionation and those receiving hypofractionation.

Discussion

In this large comparative analysis conducted in a prospective multicenter cohort of patients with breast cancer treated with adjuvant whole-breast radiotherapy after lumpectomy, we observed substantial differences by fractionation schedule in both physician-assessed and patient-reported acute toxic effects, including pain, fatigue, and skin reaction/bother during radiation treatment, but similar experiences after treatment. This suggests that the selection of radiation fractionation schedule may affect the incidence of acute, treatment-related toxic effects of adjuvant whole-breast radiotherapy, which may compromise patients' quality of life during this challenging period.

Considerable evidence has accumulated, particularly over the past decade, regarding the efficacy and safety of hypofractionated whole-breast radiation therapy. Randomized trials from Canada[1] and Great Britain[2] have demonstrated equivalent tumor control, as well as a possible reduction in late toxic effects in patients receiving hypofractionated schedules of 40 to 42.5 Gy in 15 to 16 fractions, compared with the conventional fractionation schedule of 50 Gy in 25 fractions.

The decision to reduce the total dose is related to the observation of substantial toxic effects in older studies of hypofractionated whole-breast radiotherapy that maintained total dose in conjunction with higher dose per fraction.[12] Evidence from laboratory, animal, and clinical studies suggests that fraction size has a larger impact on late effects than acute effects of radiotherapy.[26-28] The linear-quadratic model of the relationship between total isoeffective dose and dose per fraction addresses the observation that cells from late-responding tissues have survival curves that are more curved in shape (with a lower α to β ratio) than those from early-responding tissues. This means that for a

Table 3. Maximum Patient Reported Toxic Effects During the Treatment Period

Toxic Effect	Conventional Fractionation (n = 1297)	Hypofractionation (n = 426)	*P* Value[a]	Odds Ratio (95% CI)[a]
Breast pain (0-10)				
Mean (SD)	3.4 (2.7)	2.2 (2.3)		
Median (range)	3 (0-10)	2 (0-10)		
No. (%)				
None (0)	164 (12.6)	118 (27.7)	.003	1.92 (1.25-2.96)
Mild (1-3)	601 (46.3)	205 (48.1)		
Moderate (4-7)	386 (29.8)	86 (20.2)		
Severe (8-10)	146 (11.3)	17 (4.0)		
Moist desquamation, No. (%)				
Absent	964 (74.3)	410 (96.2)	<.001	4.91 (2.35-10.28)
Present	333 (25.7)	16 (3.8)		
Dry desquamation, No. (%)				
Absent	625 (48.2)	374 (87.8)	<.001	4.33 (2.49-7.53)
Present	672 (51.8)	52 (12.2)		
Bothered "All the Time" or "Often," No. (%)				
Itching of the skin of your treated breast				
No	812 (62.6)	340 (79.8)	.44	1.22 (0.73-2.03)
Yes	485 (37.4)	86 (20.2)		
Burning or stinging of the skin of your treated breast				
No	795 (61.3)	359 (84.3)	.002	2.38 (1.39-4.06)
Yes	502 (38.7)	67 (15.7)		
Skin color changes in the treated breast				
No	1062 (81.9)	375 (88.0)	.68	0.87 (0.46-1.65
Yes	235 (18.1)	51 (12.0)		
Your treated breast hurting				
No	862 (66.5)	358 (84.0)	.001	2.50 (1.44-4.33)
Yes	435 (33.5)	68 (16.0)		
Swelling of your treated breast				
No	913 (70.4)	359 (84.3)	.03	1.88 (1.08-3.28)
Yes	384 (29.6)	67 (15.7)		
The effects of your skin reaction to radiation on your interactions with others				
No	1143 (88.1)	404 (94.8)	.74	1.15 (0.51-2.61)
Yes	154 (11.9)	22 (5.2)		
The effects of your skin reaction to radiation on your daily activities				
No	1065 (82.1)	397 (93.2)	.21	1.57 (0.78-3.16)
Yes	232 (17.9)	29 (6.8)		
Your skin reaction to radiation making it hard to work or do what you enjoy				
No	1074 (82.8)	399 (93.7)	.26	1.52 (0.74-3.06)
Yes	223 (17.2)	27 (6.3)		

(continued)

Table 3. Maximum Patient Reported Toxic Effects During the Treatment Period (continued)

Toxic Effect	Conventional Fractionation (n = 1297)	Hypofractionation (n = 426)	*P* Value[a]	Odds Ratio (95% CI)[a]
In General, During the Last 4 Weeks, "Always" or "Most of the Time" Did You, No. (%)[b]				
Feel that your radiation therapy limited your daily activities?				
No	1130 (89.1)	394 (94.0)		
Yes	139 (10.9)	25 (6.0)	.68	1.19 (0.53-2.66)
Not answered	28	7		
Feel bothered by the side effects of your radiation treatment?				
No	1065 (82.1)	383 (92.5)		
Yes	201 (15.5)	31 (7.5)	.20	1.59 (0.78-3.25)
Not answered	31	12		
Feel upset about the side effects of your radiation treatment?				
No	1164 (91.9)	399 (95.9)		
Yes	102 (8.1)	17 (4.1)	.83	1.11 (0.43-2.86)
Not answered	31	10		
Feel that your radiation therapy was worth doing even with the side effects?				
No	160 (12.8)	67 (16.6)		
Yes	1089 (87.2)	336 (83.4)	.62	1.20 (0.59-2.41)
Not answered	48	23		
Think about stopping your radiation therapy?[b]				
No	1233 (98.0)	409 (98.8)		
Yes	25 (2.0)	5 (1.2)		
Not answered	39	12		
Feel significant fatigue?				
No	881 (70.3)	340 (81.2)		
Yes	373 (29.7)	79 (18.9)	.02	1.87 (1.11-3.15)
Not answered	43	7		
Feel pain in your breast or chest wall?				
No	1059 (85.2)	376 (91.5)		
Yes	184 (14.8)	35 (8.5)	.051	20.6 (1.00-4.24)
Not answered	54	15		
Worry about your skin reaction to the radiation?				
No	1020 (81.9)	378 (91.1)		
Yes	225 (18.1)	37 (8.9)	.12	1.71 (0.87-3.35)
Not answered	52	11		
Feel distressed about the appearance of your chest?				
No	1115 (89.1)	399 (95.9)		
Yes	137 (10.9)	17 (4.1)	.27	1.66 (0.67-4.05)
Not answered	45	10		

(continued)

Table 3. Maximum Patient Reported Toxic Effects During the Treatment Period (continued)

Toxic Effect	Conventional Fractionation (n = 1297)	Hypofractionation (n = 426)	*P* Value[a]	Odds Ratio (95% CI)[a]
Overall, my radiation therapy treatments have been[b]				
Very convenient	305 (24.3)	110 (26.4)	.54[c]	0.86 (0.54-1.38)[c]
Convenient	369 (29.5)	125 (30.1)		
Neutral	389 (31.1)	115 (27.6)		
Inconvenient	125 (10.0)	41 (9.9)		
Very inconvenient	64 (5.1)	25 (6.0)		
Not answered	45	10		
Overall, how bothered have you been by the amount of time it took to have your radiation therapy treatments?[b]				
Very	9 (0.7)	2 (0.5)	.58[d]	1.14 (0.71-1.86)[d]
Quite	13 (1.0)	4 (1.0)		
Moderately	84 (6.7)	13 (3.1)		
A little	280 (22.3)	97 (23.2)		
Not at all	870 (69.3)	302 (72.3)		
Not answered	41	8		
Overall, are the side effects of radiation therapy as you expected?[b]				
Much better	345 (27.5)	187 (45.0)	.25[e]	1.46 (0.76-2.79)[e]
Somewhat better	387 (30.9)	126 (30.3)		
Exactly	241 (19.2)	66 (15.9)		
Somewhat worse	243 (19.4)	35 (8.4)		
Much worse	37 (3.0)	2 (0.5)		
Not answered	44	10		
Overall, how satisfied are you with your radiation therapy treatment?[b]				
Very satisfied	727 (57.9)	266 (63.8)	.43[f]	0.72 (0.32-1.64)[f]
Satisfied	407 (32.5)	125 (30.0)		
Neutral	108 (8.6)	23 (5.5)		
Dissatisfied	2 (0.2)	1 (0.2)		
Very dissatisfied	10 (0.8)	2 (0.5)		
Not answered	43	9		
Taking everything into consideration, if given the choice again, would you decide to have radiation therapy?[b]				
Yes, definitely	785 (62.7)	272 (64.9)	.39[g]	1.38 (0.67-2.87)[g]
Probably yes	327 (26.1)	109 (26.0)		
Don't know	118 (9.4)	34 (8.1)		
Probably not	17 (1.4)	4 (1.0)		
Definitely not	6 (0.5)	0		
Not answered	44	7		

[a] Adjusted for breast volume, separation distance, body mass index, age, race, diabetes, hypertension, T stage, laterality, chemotherapy use, hormone therapy use, whether nodes were treated, mean breast dose, maximum dose to 1 cm^3 of breast volume, and whether a boost was delivered using either a cumulative logit or logistic model depending on the levels of the outcome.

[b] Reported only at end of treatment.

[c] Comparing "Very convenient" and "Convenient" vs all else between fractionation groups.

[d] Comparing any reported bother vs "Not bothered at all" between fractionation groups.

[e] Comparing "Somewhat" and "Much" worse than expected to all else between fractionation groups.

[f] Comparing "Very satisfied" and "Satisfied" vs all else between fractionation groups.

[g] Comparing "Yes, definitely" and "Probably yes" vs all else between fractionation groups.

given total dose, administration of higher doses per fraction would be expected to increase late toxic effects more substantially than acute toxic effects. Traditionally, tumors have been believed to resemble early-responding normal tissues,[29] but recently, it has become apparent that breast cancer cells may actually have an α to β ratio more similar to that seen in late-responding normal tissues,[15] meaning that equivalent tumor control might be possible in a hypofractionated regimen even if total dose were decreased.

The decreasing of total dose, in turn, might have important implications for acute toxic effects, but little clinical evidence has existed prior to the present study to document this.

The British FAST trial collected data on acute toxic effects in a subset of 327 patients, given reports of unusually severe reactions in 3 patients treated with the highly accelerated schedule of hypofractionation explored in that trial (28.5 or 30 Gy administered in 5 once-weekly fractions). The 3 reported events were deemed on review to have been neither unusual nor severe; and overall, grade 2 and 3 skin reactions appeared more frequent with conventional fractionation.[30] Documentation of the acute toxic effects of more commonly used hypofractionation schedules has been more limited. The START trials only documented that "unusually marked" acute reactions were rare and not more common with hypofractionation.[16,17] Preliminary abstract presentations from Denmark, China, Nepal, and India have been limited by small samples and measurement concerns.[31-34] Therefore, there remains considerable need for data regarding the acute toxic effects of hypofractionated radiotherapy, particularly from the patient's own perspective.

The only data available to our knowledge that describe patient-reported outcomes of hypofractionation in comparison to conventional fractionation are the preliminary results recently presented from a small randomized trial at a single institution,[35] which were consistent with the findings of this cohort study. We believe that these 2 studies complement one another (with the randomized trial offering the highest quality evidence of a causal relationship, and the present observational study offering the best external validity to generalize to real-world practice). Together, these studies offer relatively persuasive evidence that hypofractionation is indeed causally related to a reduction in acute toxic effects during breast radiation therapy, as actually practiced in the community.

The greatest strength of this study is its prospective collection of detailed clinical, toxicity, and treatment planning data from a large number of women treated in real-world radiation oncology practices. Increased awareness of the limitations of general cancer registries[36,37] in obtaining information on the very administration of radiotherapy itself, let alone the details necessary to evaluate questions relating to the comparative effectiveness of different radiation treatment approaches, has motivated growing interest in the development of radiation oncology-specific registries.[38] Although there are advantages to considering data from real-world practice and large numbers of patients from whom detailed physician-assessed and patient-reported measures have been collected, there are also associated limitations. First, the size and scope of such an endeavor as MROQC make it impossible to firmly standardize the timing of assessments beyond the immediate treatment period. Although it is reassuring that all patients included in the present analysis had an end-of-treatment evaluation, it is possible that patients treated with hypofractionation had a delayed incidence of their most severe acute toxic effects, which might have been missed as a result of the lack of a routine weekly visit after completion of treatment. We can, however, reassure the reader that there was no systematic difference in the distribution of timing of follow-up assessments by fractionation approach (eAppendix 3 in the Supplement). Moreover, we did collect information regarding toxic effects in any patients who were seen after treatment for any reason, including unscheduled short-interval toxicity management visits—so severe toxic effects prompting a visit would have been noted in the follow-up period. The general infrequency of toxic effects during the follow-up period and the similarities across numerous outcome measures for patients treated with each fractionation approach suggest that major differences in posttreatment toxicities are unlikely. Still, further research would be useful to explore posttreatment toxic effects in greater detail, including verification of the observation of a slightly higher rate of induration (albeit mostly mild) in the hypofractionation subgroup during follow-up in this study.

Another limitation of this study relates to its observational nature; patients were not randomly allocated to hypofractionation vs conventional fractionation, and most patients were treated with conventional fractionation. Some of the factors that affect selection of fractionation (including smaller body habitus and lack of chemotherapy administration) may themselves affect likelihood of acute toxic effects, such that the association observed might be confounded rather than causal. Nevertheless, MROQC includes information on many potential confounding factors, and the associations observed persisted even after adjustment for all of these. That these results are consistent with those of a randomized trial suggests that the associations observed are likely to be causal in nature. The main strength of this study is its ability to complement the findings of randomized trials to demonstrate that acute toxic effects seem to be less frequent and/or severe with hypofractionation as applied in routine practice in the community.

The slow and nonuniform uptake of hypofractionated breast radiotherapy has recently become the subject of considerable attention.[9-11,39] Studies have shown that hypofractionation remains underused, even in analyses of patients treated well after the issuance of consensus guidelines,[3] mature long-term evidence from clinical trials, and the encouragement of the American Society for Radiation Oncology's Choosing Wisely campaign.[4] It is critical to recognize that hypofractionation not only provides equivalent long-term tumor control in selected patients at considerably lower cost and greater convenience, but it may also represent a more tolerably administered approach. Patients and physicians who may be cautious about embracing new techniques should consider carefully the evidence in the present study. Reducing the severity and frequency of acute toxic effects from breast radiotherapy has been cited as the justification for costly and complex treatment planning approaches, including intensity-modulated radiotherapy. The present results are striking insofar as they suggest that similar or even greater gains in tolerability might be possible with a simple adjustment to dosing schedules that is also less costly and more convenient.

Conclusions

This study provides information about the frequency and nature of acute toxic effects during whole-breast hypofrac-

tionated radiotherapy, highly relevant to women considering this treatment and absent from the literature to date. Given the importance of patient-reported outcomes and generalizable evidence of comparative effectiveness from patients treated outside the context of clinical trials, it provides a complement to the findings of randomized trials and encourages enthusiasm for this innovative approach.

ARTICLE INFORMATION

Accepted for Publication: June 10, 2015.

Published Online: August 6, 2015. doi:10.1001/jamaoncol.2015.2590.

Author Contributions: Dr Jagsi and Mr Griffith had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Jagsi, Griffith, Boike, Walker, Nurushev, Grills, Moran, Feng, Pierce.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Jagsi, Griffith.
Critical revision of the manuscript for important intellectual content: Griffith, Boike, Walker, Nurushev, Grills, Moran, Feng, Hayman, Pierce.
Statistical analysis: Griffith.
Obtained funding: Pierce.
Administrative, technical, or material support: Boike, Grills, Moran.
Study supervision: Pierce.

Conflict of Interest Disclosures: None reported.

Funding/Support: Funding for MROQC is provided by Blue Cross Blue Shield of Michigan (BCBSM) and Blue Care Network. The BCBSM Value Partnerships program (http://www.valuepartnerships.com) provides clinical and executive support for all Collaborative Quality Initiatives programs.

Role of the Funder/Sponsor: The funding organization hosts regular meetings of consortium participants and provides financial support to participating radiation oncology practices for data collection and to the University of Michigan for data analysis, but it had no role in the design or conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The authors gratefully acknowledge the contributions of all members of the MROQC consortium, without whose participation these data would not be available. Specifically, we acknowledge David Share, MD, and Marc Keshishian, MD, of BCBSM, for supporting and guiding the development of MROQC. Neither was compensated beyond their salary for their contribution.

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