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original reports

Toward Improving Patients' Experiences of Acute Toxicity From Breast Radiotherapy: Insights From the Analysis of Patient-Reported Outcomes in a Large Multicenter Cohort

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abstract

PURPOSE Understanding acute toxicities after whole-breast radiotherapy is important to inform patients, guide treatment decisions, and target supportive care. We evaluated patient-reported outcomes prospectively collected from a cohort of patients with breast cancer.

METHODS We describe the maximal toxicity reported by 8,711 patients treated between 2012 and 2019 at 27 practices. Multivariable models identified characteristics associated with (1) breast pain, (2) bother from itching, stinging/burning, swelling, or hurting of the treated breast, and (3) fatigue within 7 days of completing whole-breast radiotherapy.

RESULTS Moderate or severe breast pain was reported by 3,233 (37.1%): 1,282 (28.9%) of those receiving hypofractionation and 1,951 (45.7%) of those receiving conventional fractionation. Frequent bother from at least one breast symptom was reported by 4,424 (50.8%): 1,833 (41.3%) after hypofractionation and 2,591 (60.7%) after conventional fractionation. Severe fatigue was reported by 2,008 (23.1%): 843 (19.0%) after hypofractionation and 1,165 (27.3%) after conventional fractionation. Among patients receiving hypofractionated radiotherapy, younger age ($P < .001$), higher body mass index (BMI; $P < .001$), Black ($P < .001$) or other race ($P = .002$), smoking status ($P < .001$), larger breast volume ($P = .002$), lack of chemotherapy receipt ($P = .004$), receipt of boost treatment ($P < .001$), and treatment at a nonteaching center predicted breast pain. Among patients receiving conventionally fractionated radiotherapy, younger age ($P < .001$), higher BMI ($P = .003$), Black ($P < .001$) or other race ($P = .002$), diabetes ($P = .001$), smoking status ($P < .001$), and larger breast volume ($P < .001$) predicted breast pain.

CONCLUSION In this large observational data set, substantial differences existed according to radiotherapy dose fractionation. Race-related differences in pain existed despite controlling for multiple other factors; additional research is needed to understand what drives these differences to target potentially modifiable factors. Intensifying supportive care may be appropriate for subgroups identified as being vulnerable to greater toxicity.

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ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Meta-analysis of randomized trials has demonstrated convincingly that radiation therapy provides substantial benefits in local control and modest improvements in survival for many patients with early-stage breast cancer.[1] Radiotherapy is also known to cause both acute and late toxicity. Acute effects include fatigue and radiation dermatitis, and inflammatory symptoms may bother patients. Prior work[2] has demonstrated that acute toxicity appears less frequently with the moderately hypofractionated schedules that are now guideline supported for most node-negative patients undergoing breast-conserving surgery.[3] Nevertheless, nearly one half of all patients may experience grade 2 or greater acute toxicity even with these newer approaches.[4]

Patients often have fears about radiation-related toxicity.[5-8] In one recent survey, 19% of patients with breast cancer felt they lacked sufficient information about the adverse effects to expect, and 32% indicated experiencing adverse effects that they wished they had known more about.[9] Although some of this might be remediated by greater attention to physician-patient communication, the ability to fully inform patients is limited by gaps in the existing literature. Currently, there is a paucity of information that

CONTEXT

Key Objective

To understand patient experiences with acute toxicity after whole-breast radiotherapy in a large multicenter cohort of patients with breast cancer treated in the United States between 2012 and 2019.

Knowledge Generated

We found that patients receiving moderately hypofractionated whole-breast radiotherapy reported considerably less acute toxicity. Race-related differences in pain experiences existed despite controlling for multiple other factors, with worse pain among women who were Black or whose race was defined as "other" (not White, Asian, or Black).

Relevance

These findings are useful to inform patients, guide treatment decisions, and target supportive care.

characterizes the experiences of radiation toxicity from the perspective of the patients themselves.[10] Moreover, beyond the impact of fractionation, little is known about whether certain subgroups of patients (on the basis of treatment characteristics or underlying factors) may have higher risks of toxicity after whole-breast irradiation.

Because an understanding of acute patient-reported toxicities after breast radiotherapy would be valuable to inform patients, guide treatment decisions, and target supportive care interventions, we evaluated patient-reported outcomes in a statewide multicenter consortium, including prospectively collected data from a large cohort of women with breast cancer who received whole-breast radiotherapy after breast-conserving surgery.

METHODS

Data Collection and Sample

As part of a collaborative quality improvement initiative, the Michigan Radiation Oncology Quality Consortium (MROQC) prospectively collects clinical, dosimetric, and patient-reported outcomes data from women treated for breast cancer at 27 practices, together with information about facilities and providers.[11] Eligible patients during the study period were those being treated with adjuvant whole-breast radiotherapy for nonmetastatic, unilateral breast cancer at an MROQC-participating institution.

This effort is institutional review board approved as a collaborative quality initiative; clinical information on all eligible patients is entered into the database, but patient participation in surveys is voluntary (with written consent documentation waived). Practices are provided with staff support, funded by Blue Cross Blue Shield of Michigan, to gather data on all patients treated with lumpectomy and unilateral whole-breast radiotherapy, regardless of insurer. Those practices that meet the quality benchmarks are provided with a "gold card" certification that eliminates the need for prior authorization for treatment if the patient is insured by Blue Cross Blue Shield of Michigan.

A total of 12,577 patients were treated with lumpectomy and whole-breast radiotherapy at MROQC sites and had data entered into the MROQC database between January 1, 2012, and September 30, 2019. We describe here the maximal toxicity reported by the 8,711 patients who provided survey responses within 7 days before or after the end of treatment and for whom we had sufficient data to determine dose fractionation and treatment fields.

Measures

Three primary predefined outcomes of interest were measured: (1) breast pain, (2) bother (related to itching, stinging/burning, swelling, or hurting of the treated breast), and (3) fatigue, defined using the maximum value recorded on any on-treatment weekly evaluation or on the end-of-treatment evaluation. Specifically, breast pain was assessed using an approved modification of the Brief Pain Inventory[12] that asks patients to rate their pain during the last 24 hours at its worst, least, average, and "right now." Breast pain was considered moderate or severe when the score on any one of those four items was ≥ 4 on the 10-point scale.

Bother was measured using a modified scaled measure adapted from the Skindex[13] to include four symptoms of interest (itching of the skin of the treated breast, burning or stinging of the skin of the treated breast, swelling of the treated breast, and hurting of the treated breast). Patients were asked, "During the past week, how often have you been bothered by…" for each symptom, with response options of "never," "rarely," "sometimes," "often," or "all the time." Bother was considered frequent when the score was "often" or "all the time" for any of the four subitems. Fatigue was measured as in prior work[2] with a single item asking, "How often did you feel significant fatigue?" and was considered severe when rated as present "always" or "most of the time" (rather than "sometimes," "rarely," or "never") over the past 4 weeks.

The patient characteristics analyzed included age (grouped as < 50 years, 50-59 years, 60-69 years, or ≥ 70 years), body mass index (BMI; grouped as < 18.5, 18.5 to < 25,

25 to < 30, 30 to < 35, 35 to < 40, and ≥ 40), race (defined by self-report where available and otherwise by clinician report, and grouped as White, Black, Asian, or other, with the "other" category including categories of American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, Arab/Middle Eastern, or other),[14] hypertension (yes or no), diabetes (yes or no), smoking status (never, former, or current smoker), and chemotherapy receipt (yes or no). Physical measures of body habitus included from treatment planning scans were separation distance from medial and lateral tangential beam entry (continuously measured in centimeters) and breast volume (continuously measured in cubic centimeters). Radiation treatment technique characteristics that were included were the use of a supraclavicular field (with or without additional regional fields) for radiotherapy (yes/no), fractionation (conventional fractionation *v* hypofractionation, defined as using a dose per fraction of 2.5 Gy or larger), and use of boost (yes/no).

Analytic Approach

We first described the outcomes of interest separately for patients treated with conventional fractionation and those treated with hypofractionation, given prior work suggesting that these two groups had substantially different rates of acute toxicity. Multilevel multivariable logistic regression models separately identified the patient-level individual and treatment characteristics associated with (1) breast pain, (2) a bother scale (related to itching, stinging/burning, swelling, or hurting of the treated breast), and (3) fatigue. Patients were clustered within institution, with institution associated as a random effect and whether the institution teaches residents/medical students as the sole institution-level covariable. Given that the use of a supraclavicular field was almost exclusive to patients receiving conventional fractionation, we constructed multivariable models of each of the three outcomes separately for conventionally fractionated cases and hypofractionated cases after excluding 15 hypofractionated cases in which a supraclavicular field was used. *P* values ≤ 5% were considered significant, and all analyses were conducted using the SAS System, version 9.4 (Cary, NC).

RESULTS

The characteristics of the study sample are reported for 4,268 conventionally fractionated and 4,443 hypofractionated cases in Table 1. Of patients receiving hypofractionation, 82.5% were White and 14.3% were Black; of patients receiving conventional fractionation, 77.0% were White and 19.1% were Black. Chemotherapy was known to have been received by 15.9% of those receiving hypofractionation and 44.3% of those receiving conventional fractionation.

Table 2 lists the frequencies of the three main outcomes (and breakdown of the bother subitems) by fractionation. Moderate or severe breast pain was reported by 3,233 (37.1%): 1,282 (28.9%) of those receiving hypofractionation and 1,951 (45.7%) of those receiving conventional fractionation. Frequent bother from at least one breast symptom was reported by 4,424 (50.8%): 1,833 (41.3%) after hypofractionation and 2,591 (60.7%) after conventional fractionation. Severe fatigue was reported by 2,008 (23.1%): 843 (19.0%) after hypofractionation and 1,165 (27.3%) after conventional fractionation.

Figure 1 presents in its three panels the results of the multivariable models of the three outcomes of interest among patients receiving hypofractionated radiotherapy; detailed model results are presented in Appendix Table A1 (online only). Patient-level factors independently and significantly associated with moderate or severe breast pain were younger age ($P < .001$), higher BMI ($P < .001$), Black ($P < .001$) or other race ($P = .002$), former or current smoking status ($P < .001$), and larger breast volume ($P = .002$). Lack of receipt of chemotherapy ($P = .004$) and receipt of boost treatment ($P < .001$) also predicted breast pain. Treatment at a teaching center ($P = .009$) predicted less breast pain. Factors independently and significantly associated with frequent bother from breast symptoms were younger age ($P < .001$), higher BMI ($P < .001$), Black race ($P = .002$), former or current smoking status ($P < .001$), breast volume ($P < .001$), and separation distance ($P = .04$). Lack of receipt of chemotherapy ($P < .001$) and receipt of boost treatment ($P < .001$) also predicted bother from breast symptoms. Factors independently and significantly associated with severe fatigue were younger age ($P < .001$), higher BMI ($P < .001$), Asian race ($P = .004$), and former or current smoking status ($P < .001$). Treatment and dosimetric parameters were not independently associated with fatigue among patients treated with hypofractionation.

Figure 2 presents in its three panels the results of the multivariable models of the three outcomes of interest among patients receiving conventionally fractionated radiotherapy detailed model results are presented in Appendix Table A2 (online only). Factors independently and significantly associated with moderate or severe breast pain were younger age ($P < .001$), higher BMI ($P = .003$), Black ($P < .001$) or other race ($P = .002$), diabetes ($P = .001$), current or former smoking status ($P < .001$), and larger breast volume ($P < .001$). Factors independently and significantly associated with frequent bother from breast symptoms were younger age ($P < .001$), Black ($P = .003$) or other race ($P = .004$), hypertension ($P < .001$), diabetes ($P < .001$), current or former smoking status ($P < .001$), breast volume ($P < .001$), and separation distance ($P = .01$). Lack of receipt of chemotherapy ($P = .007$) and use of a supraclavicular field ($P = .006$) but not boost also predicted bother from breast symptoms among patients receiving conventional fractionation. Factors independently and significantly

TABLE 1. Sample Description: Stratified by Fractionation Scheme

Variable/Level	Total	Hypofractionation	Conventional Fractionation
Age group, years			
< 50	1,420 (16.30)	443 (9.97)	977 (22.89)
50-59	2,522 (28.95)	1,181 (26.58)	1,341 (31.42)
60-69	2,937 (33.72)	1,622 (36.51)	1,315 (30.81)
≥ 70	1,832 (21.03)	1,197 (26.94)	635 (14.88)
BMI category, kg/m^2			
Underweight, < 18.5	147 (1.69)	63 (1.42)	84 (1.97)
Normal, 18.5 to < 25	1,984 (22.78)	1,043 (23.48)	941 (22.05)
Overweight, 25 to < 30	2,660 (30.54)	1,486 (33.45)	1,174 (27.51)
Obesity I, 30 to < 35	1,991 (22.86)	1,019 (22.93)	972 (22.77)
Obesity II, 35 to < 40	1,086 (12.47)	494 (11.12)	592 (13.87)
Obesity III, > 40	843 (9.68)	338 (7.61)	505 (11.83)
Breast volume, mL, continuous, mean (SD) [range]	1,154.1 (699.31) [0.00-18,224.00]	1,074.5 (624.67) [0.00-14,338.90]	1,230.9 (756.55) [1.20-18,224.00]
Separation distance, cm, continuous, mean (SD) [range]	22.73 (3.90) [10.00-42.00]	22.29 (3.70) [10.00-42.00]	23.19 (4.04) [10.00-40.83]
Race			
White	6,952 (79.81)	3,667 (82.53)	3,285 (76.97)
Black	1,452 (16.67)	635 (14.29)	817 (19.14)
Asian	137 (1.57)	57 (1.28)	80 (1.87)
Other	170 (1.95)	84 (1.89)	86 (2.01)
Hypertension			
No	4,706 (54.02)	2,350 (52.89)	2,356 (55.20)
Yes	4,005 (45.98)	2,093 (47.11)	1,912 (44.80)
Diabetes			
No	7,393 (84.87)	3,794 (85.39)	3,599 (84.33)
Yes	1,318 (15.13)	649 (14.61)	669 (15.67)
Smoking status			
Never smoker	5,052 (58.00)	2,586 (58.20)	2,466 (57.78)
Former smoker	2,724 (31.27)	1,422 (32.01)	1,302 (30.51)
Current smoker	935 (10.73)	435 (9.79)	500 (11.72)
Chemotherapy			
Not reported	80 (0.92)	45 (1.01)	35 (0.82)
No	6,038 (69.31)	3,694 (83.14)	2,344 (54.92)
Yes	2,593 (29.77)	704 (15.85)	1,889 (44.26)
Boost			
No	1,456 (16.71)	1,215 (27.35)	241 (5.65)
Yes	7,255 (83.29)	3,228 (72.65)	4,027 (94.35)
Supraclavicular field			
No	7,767 (89.16)	4,428 (99.66)	3,339 (78.23)
Yes	944 (10.84)	15 (0.34)	929 (21.77)
Institution teaching status			
No	5,523 (63.40)	2,851 (64.17)	2,672 (62.61)
Yes	3,188 (36.60)	1,592 (35.83)	1,596 (37.39)

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviations: BMI, body mass index; SD, standard deviation.

TABLE 2. Distribution of Patient-Reported Breast Pain, Bother, and Fatigue

Variable/Level	Total	Hypofractionation	Conventional Fractionation
Pain rating maximum			
Continuous, 0-10, mean (SD) [range]	3.13 (2.70) [0.00-10.00]	2.56 (2.45) [0.00-10.00]	3.71 (2.83) [0.00-10.00]
Pain rating maximum level			
None	1,516 (17.40)	990 (22.28)	526 (12.32)
Mild	3,962 (45.48)	2,171 (48.86)	1,791 (41.96)
Moderate	1,952 (22.41)	878 (19.76)	1,074 (25.16)
Severe	1,281 (14.71)	404 (9.09)	877 (20.55)
Frequent bother with itching			
Missing	6 (0.07)	6 (0.14)	0 (0.00)
No	5,930 (68.07)	3,369 (75.83)	2,561 (60.00)
Yes	2,775 (31.86)	1,068 (24.04)	1,707 (40.00)
Frequent bother with stinging			
No	6,111 (70.15)	3,579 (80.55)	2,532 (59.33)
Yes	2,600 (29.85)	864 (19.45)	1,736 (40.67)
Frequent bother with hurting			
No	6,236 (71.59)	3,529 (79.43)	2,707 (63.43)
Yes	2,475 (28.41)	914 (20.57)	1,561 (36.57)
Frequent bother with swelling			
No	6,594 (75.70)	3,570 (80.35)	3,024 (70.85)
Yes	2,117 (24.30)	873 (19.65)	1,244 (29.15)
Frequent bother from any breast symptom			
No	4,287 (49.21)	2,610 (58.74)	1,677 (39.29)
Yes	4,424 (50.79)	1,833 (41.26)	2,591 (60.71)
Severe fatigue			
Missing	750 (8.61)	393 (8.85)	357 (8.36)
No	5,953 (68.34)	3,207 (72.18)	2,746 (64.34)
Yes	2,008 (23.05)	843 (18.97)	1,165 (27.30)

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviation: SD, standard deviation.

associated with severe fatigue were younger age ($P < .001$), higher BMI ($P = .02$), diabetes ($P = .003$), former smoking status ($P = .006$), and separation distance ($P = .011$). Treatment and dosimetric parameters were not significantly independently associated with fatigue among patients treated with conventional fractionation. Figure 3 presents the frequencies of the three main outcomes by race for conventional and hypofractionated cases, respectively.

DISCUSSION

This large multicenter study quantifies patient-reported experiences of pain, bother from breast symptoms, and fatigue within 7 days of completing modern whole-breast radiotherapy for breast cancer. This information is critically important to inform patients who desire realistic information about the likelihood of acute treatment-related toxicity in their own individual circumstances. Several important insights about patient and treatment factors associated with toxicity emerged. Not only did outcomes differ by radiotherapy approach, including dose fractionation, boost treatment, and regional nodal irradiation, but acute toxicity also varied by body habitus, age, race, smoking behavior, and comorbidities, with most factors consistent regardless of which fractionation schedule was used.

Radiotherapy approaches that were associated with higher acute toxicity included conventional fractionation, boost radiotherapy among those receiving hypofractionation, and regional nodal irradiation among those receiving conventional fractionation. The substantial differences observed according to fractionation approach are consistent with the findings of smaller prior reports and provide additional support for efforts to ensure that all women for whom evidence exists to support the use of moderate hypofractionation are provided this option for treatment.[14,15] The observation that toxicity was higher in patients who received

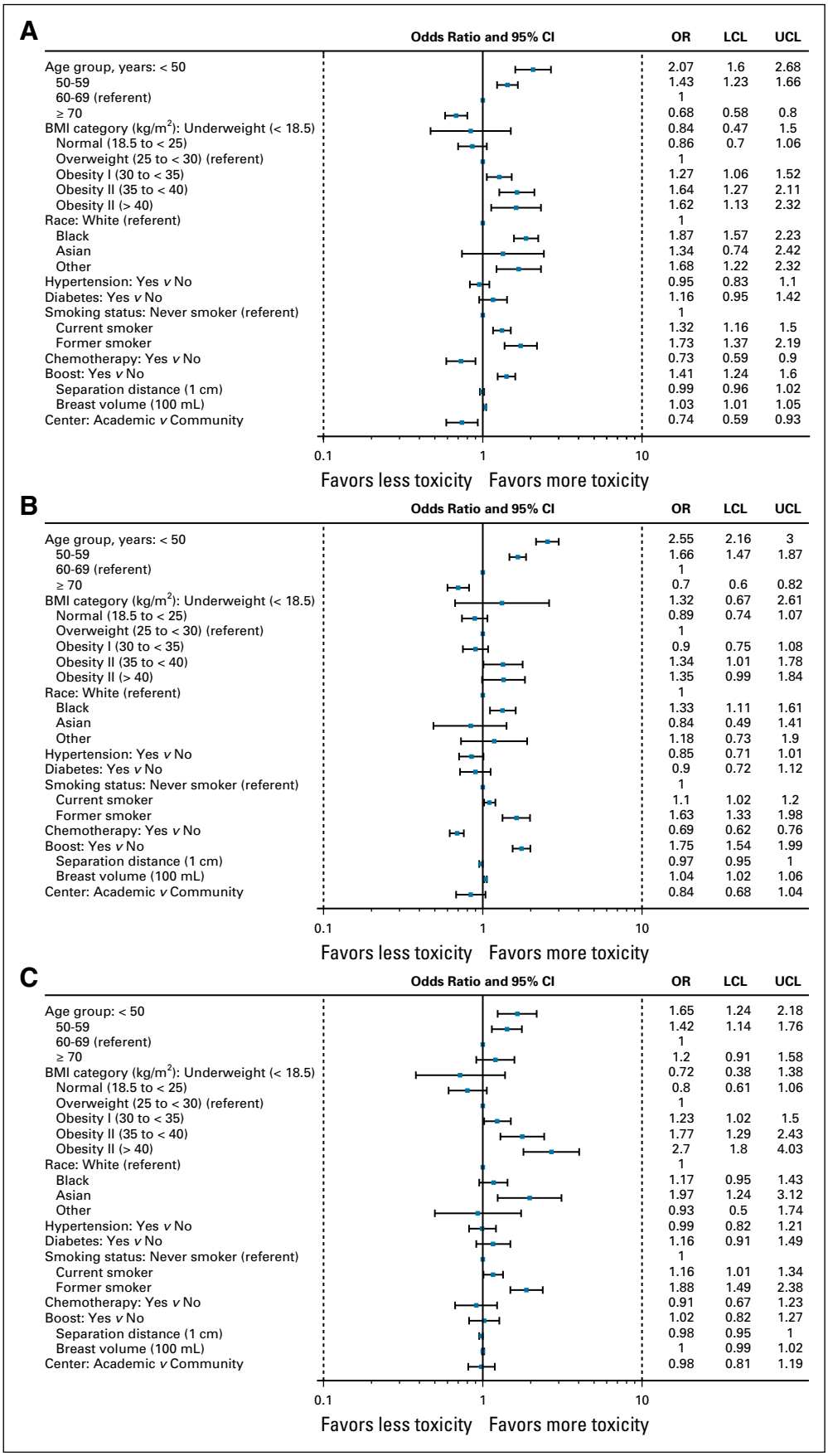

FIG 1. Results of three multivariable models of patient-reported acute toxicity experiences among 4,428 patients treated with hypofractionated whole-breast radiation therapy (and without supraclavicular fields). (A) Moderate or severe breast pain. (B) Frequent bother from breast symptoms. (C) Severe fatigue. BMI, body mass index; CL, confidence limit; LCL, Lower Confidence Limit; OR, odds ratio; UCL, Upper Confidence Limit.

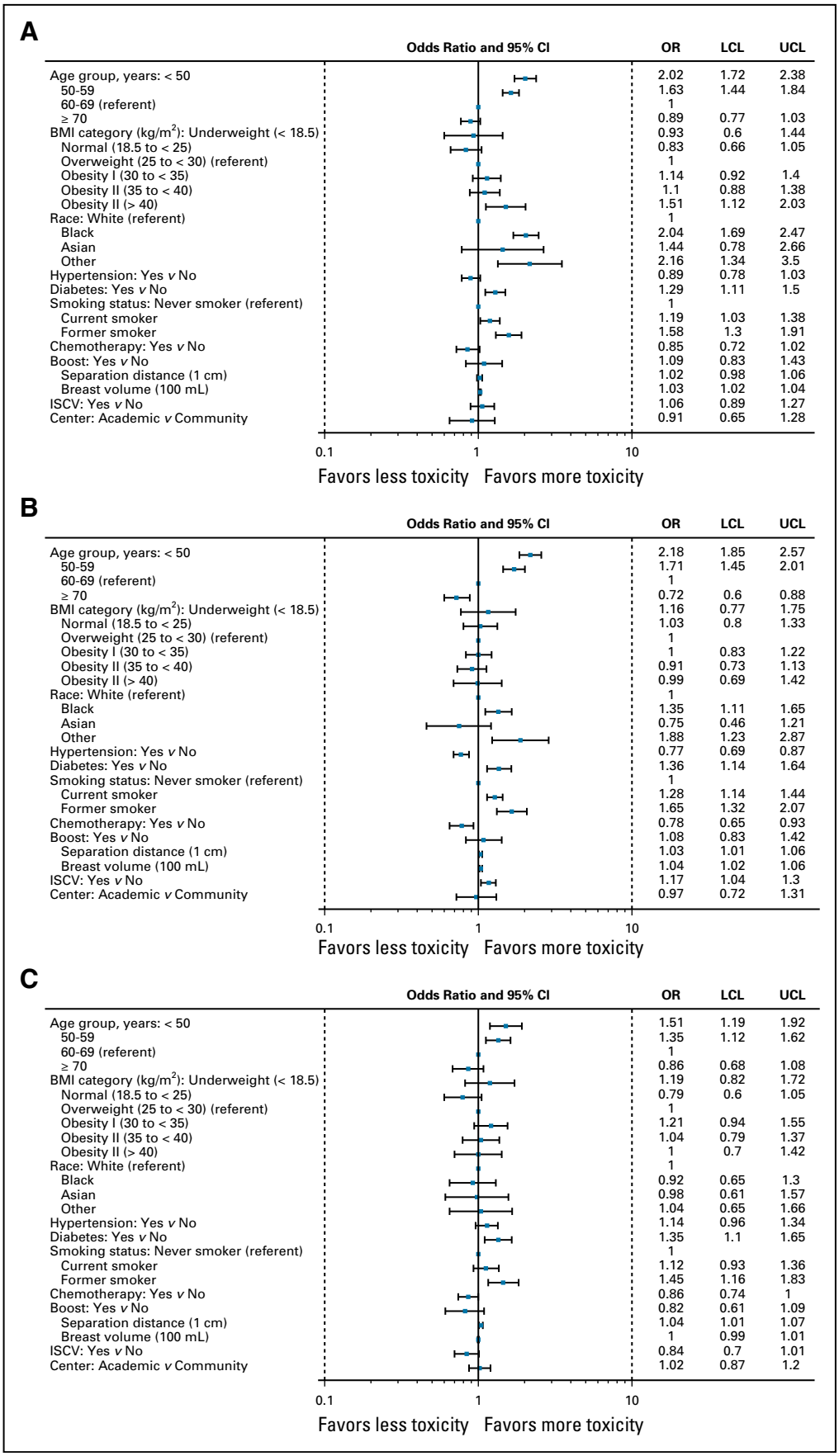

FIG 2. Results of three multivariable models of patient-reported acute toxicity experiences among 4,268 patients treated with conventionally fractionated whole-breast radiation therapy (either with or without supraclavicular fields). (A) Moderate or severe breast pain. (B) Frequent bother from breast symptoms. (C) Severe fatigue. BMI, body mass index; CL, confidence limit; iSCV, Irradiated Supraclavicular Lymph Nodes; LCL, Lower Confidence Limit; OR, odds ratio; UCL, Upper Confidence Limit.

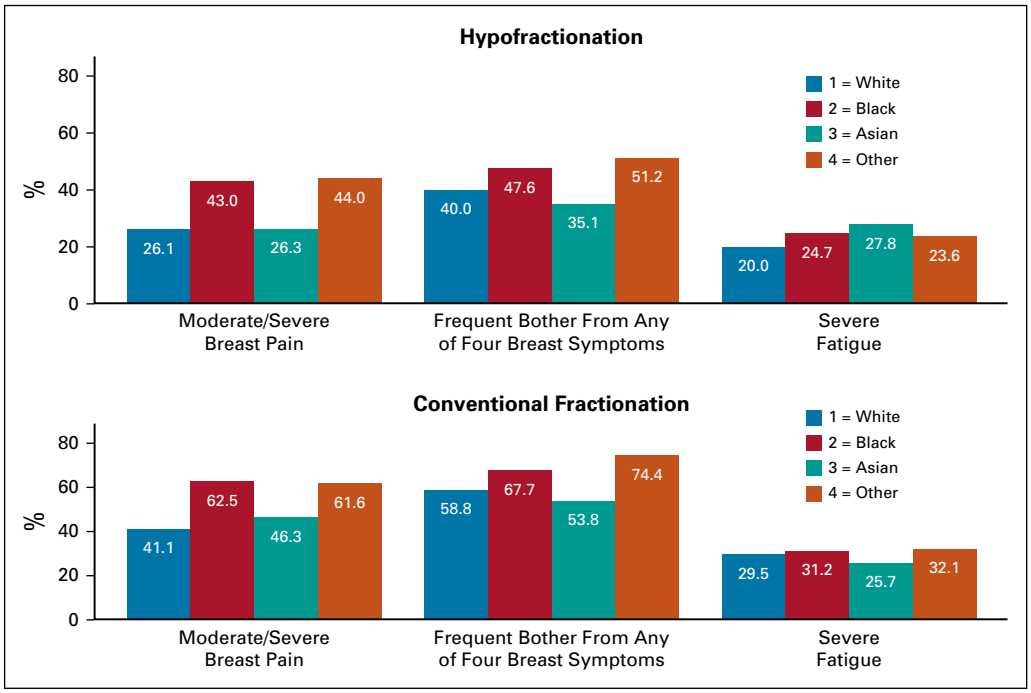

FIG 3. Frequency of patient-reported acute toxicity after breast radiotherapy, by fractionation and race.

boost radiotherapy, but only among those receiving hypofractionated whole-breast radiotherapy, is intriguing. This may reflect a true causal impact of boost treatment in increasing toxicity in that setting, although it is also possible that the additional week of observation in patients receiving boost dose drives the difference observed, if acute toxicity tends to manifest primarily after 3 weeks, as is plausible given the transit time of the basal layer of the epidermis. Additional research, including evaluation of patient experiences soon after completion of radiotherapy, as is now being collected on a standard basis by the MROQC, will be important in developing a more definitive understanding of this observation. For now, this observation suggests that efforts to delineate which patients derive meaningful benefit from boost radiotherapy are important. Finally, the observation of increased bother from breast symptoms among patients who received regional nodal irradiation (who in this analytic data set were all treated with conventional fractionation) suggests that discussion of acute toxicity is relevant to include when guiding patients for whom the indications for regional nodal irradiation are ambiguous. It also heightens the need for enrollment in trials such as NRG B-51[16] and NCIC MA-39,[17] which seek to identify patients in whom regional nodal irradiation can safely be omitted, either because of excellent response to neoadjuvant therapy in the case of B-51 or because of inherently favorable biologic features in the case of MA-39.

Several patient characteristics also correlated with the patient-reported acute toxicity outcomes measured here. One risk factor was larger body habitus (as measured by BMI and by dosimetric parameters of separation distance and breast volume). The higher rates of bother from breast symptoms and pain in these patients likely relate to skin and soft tissue reactions that develop in these patients. These reactions result from the physical properties of megavoltage beams used for modern radiotherapy administration that make obtaining dose homogeneity more challenging in larger patients, together with the "auto-bolus effect," which increases skin dose in skin folds, where there may also be additional damage because of friction. The association of larger habitus with fatigue is intriguing; research should investigate whether a greater volume of irradiated tissue leads to higher levels of inflammatory cytokine release and helps identify targets for prevention and management of treatment-related fatigue. These findings should also motivate ongoing research to identify best dosimetric practices and whether alternative techniques, including partial breast irradiation, which has recently been found to result in minimal if any differences in disease control,[18-20] may be particularly useful in this patient population. They also suggest the importance of exploring how to improve supportive care, perhaps by including additional nursing visits beyond the routine once-per-week physician examinations standard in radiation oncology practice, to address the substantial symptoms these patients experience.

Other groups of patients who may benefit from greater supportive care as they undergo radiation after breast-conserving surgery are those of a younger age and Black race. Whether the increased rates of toxicity reported in

these patient groups reflect inherent biologic or socially constructed socioeconomic differences of the patients themselves or differences in provider and/or patient behavior merits additional attention. There is some reason to believe that biologic differences may explain some of the differences observed according to race; prior studies have suggested that the frequency of genes involved in inflammation, wound repair, and fibrotic response to radiation vary by race, although these studies have focused primarily on genes related to late toxicity.[21,22] There is also reason to fear that social differences may explain other aspects of the differences observed, especially if patients who are Black or younger have, for example, less secure finances to acquire supportive medications and topical therapies.

Differences in provider behavior may also play a role in explaining the race-related differences observed herein. A litany of worrisome studies have shown providers to be less sensitive to the pain of Black patients and less likely to prescribe pain medication to them.[23-31] One recent study revealed that "false beliefs about biological differences between blacks and whites (e.g., 'black people's skin is thicker than white people's skin')"[32(p 4296)] were endorsed not only by White laypersons but also by one half of a sample of White medical students and residents. Moreover, those who endorsed the false beliefs were found to demonstrate racial bias in the accuracy of their pain treatment recommendations.[32] Additional research is necessary to determine the extent to which differences detected in the current study reflect differences in provider beliefs and behaviors and how best to mitigate bias in care delivery. In any case, this study substantially advances the understanding of how race does indeed seem to relate to the experience of acute toxicity of whole-breast radiotherapy, given that prior research has been limited to much smaller cohorts yielding mixed findings.[33,34] Of great importance, however, is that these findings should not be taken as a reason to dissuade Blacks from receiving breast conservation as an approach to breast cancer management; rather, they should motivate efforts to optimize supportive care.

In addition, observations of higher toxicity among smokers and those with the comorbidities of hypertension and diabetes also merit note. Whether these might be modifiable by smoking cessation or by tighter medical management of the underlying comorbidities are important questions for additional research. Intensifying supportive management is also important for these patient groups.

Finally, the observation that pain among patients treated with hypofractionation was lower when they received treatment at a teaching facility merits additional investigation. Future research should seek to identify which aspects of care, such as differences in treatment planning or toxicity management, at the academic institutions in this study might explain why patients treated in those settings had less pain. In this way, best practices to minimize pain could be generalized.

Although this study has the strengths of prospectively collecting patient-reported outcomes from a large number of individuals in a multicenter setting reflecting modern real-world practice in the United States, it also has several limitations. First, as in any observational study, associations cannot be taken to imply causation. Unmeasured confounding factors may exist. Second, although a high proportion of all eligible patients treated during the study period participated, selection effects may also have biased our findings. Third, because virtually no patients received regional nodal irradiation in combination with hypofractionation, we were unable to evaluate whether supraclavicular fields increase toxicity among patients treated with hypofractionation. Fourth, all data in the current study reflect patient self-report and may differ from physician-reported toxicity; although some consider patient-reported outcomes to be the gold standard, some might consider such data to be subjective.[35] We nevertheless believe that the patient's perspective provides irreplaceable information that other patients would value as a reference for what they might expect to experience. Fifth, differences in pain or fatigue among patient groups may have existed before radiation. Finally, we lacked information on when symptoms subsided.

In this large observational study of patient-reported toxicities after whole-breast radiotherapy, substantial differences existed not only according to radiotherapy dose fractionation but also according to a number of other patient personal and treatment characteristics. Of particular concern, race-related differences in breast pain and bother existed despite controlling for multiple other factors, including age, body habitus, comorbidities, and treatment characteristics. Additional research is needed to understand the factors that drive these and other differences detected in the current study, to target those that are potentially modifiable. Intensification of supportive care may also be appropriate for subgroups identified as being vulnerable to greater toxicity. Clinical trials must recruit diverse patients to ensure that they adequately capture toxicity experiences.

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SUPPORT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Toward Improving Patients' Experiences of Acute Toxicity From Breast Radiotherapy: Insights From the Analysis of Patient-Reported Outcomes in a Large Multicenter Cohort

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APPENDIX

TABLE A1. Multilevel Multivariable Models Explaining Toxicities for the Hypofractionated Cases (After Excluding 15 Cases With Supraclavicular Fields), With Patients Clustered Within Institution

	Moderate to Severe Breast Pain		Frequent Bother		Severe Fatigue	
Variable/Level	**OR (95% CI)**	***P*[a]**	**OR (95% CI)**	***P*[a]**	**OR (95% CI)**	***P*[a]**
Patient-level variable/level						
Age group, years		< .001[b]		< .001[b]		< .001[b]
< 50	2.07 (1.60 to 2.68)	< .001	2.55 (2.16 to 3.00)	< .001	1.65 (1.24 to 2.18)	< .001
50-59	1.43 (1.23 to 1.66)	< .001	1.66 (1.47 to 1.87)	< .001	1.42 (1.14 to 1.76)	.002
60-69 (referent)	1		1		1	
≥ 70	0.68 (0.58 to 0.80)	< .001	0.70 (0.60 to 0.82)	< .001	1.20 (0.91 to 1.58)	.19
BMI category, kg/m^2		.003[b]		< .001[b]		< .001[b]
Underweight, < 18.5	0.84 (0.47 to 1.50)	.56	1.32 (0.67 to 2.61)	.42	0.72 (0.38 to 1.38)	.33
Normal, 18.5 to < 25	0.86 (0.70 to 1.06)	.16	0.89 (0.74 to 1.07)	.22	0.80 (0.61 to 1.06)	.12
Overweight, 25 to < 30 (referent)	1		1		1	
Obesity I, 30 to < 35	1.27 (1.06 to 1.52)	.009	0.90 (0.75 to 1.08)	.25	1.23 (1.02 to 1.50)	.03
Obesity II, 35 to < 40	1.64 (1.27 to 2.11)	< .001	1.34 (1.01 to 1.78)	.04	1.77 (1.29 to 2.43)	< .001
Obesity III, > 40	1.62 (1.13 to 2.32)	.009	1.35 (0.99 to 1.84)	.06	2.70 (1.80 to 4.03)	< .001
Race		< .001[b]		.002[b]		.004[b]
White (referent)	1		1		1	
Black	1.87 (1.57 to 2.23)	< .001	1.33 (1.11 to 1.61)	.003	1.17 (0.95 to 1.43)	.14
Asian	1.34 (0.74 to 2.42)	.33	0.84 (0.49 to 1.41)	.50	1.97 (1.24 to 3.12)	.004
Other	1.68 (1.22 to 2.32)	.002	1.18 (0.73 to 1.90)	.50	0.93 (0.50 to 1.74)	.82
Hypertension						
Yes *v* No	0.95 (0.83 to 1.10)	.53	0.85 (0.71 to 1.01)	.06	0.99 (0.82 to 1.21)	.95
Diabetes						
Yes *v* No	1.16 (0.95 to 1.42)	.14	0.90 (0.72 to 1.12)	.35	1.16 (0.91 to 1.49)	.23
Smoking status		< .001[b]		< .001[b]		< .001[b]
Never smoker (referent)	1		1		1	
Former smoker	1.32 (1.16 to 1.50)	< .001	1.10 (1.02 to 1.20)	.02	1.16 (1.01 to 1.34)	.04
Current smoker	1.73 (1.37 to 2.19)	< .001	1.63 (1.33 to 1.98)	≤ .001	1.88 (1.49 to 2.38)	< .001
Chemotherapy						
Yes *v* No	0.73 (0.59 to 0.90)	.004	0.69 (0.62 to 0.76)	< .001	0.91 (0.67 to 1.23)	.53
Boost						
Yes *v* No	1.41 (1.24 to 1.60)	≤ .001	1.75 (1.54 to 1.99)	< .001	1.02 (0.82 to 1.27)	.85
Separation distance, centered at 22 cm, continuous	0.99 (0.96 to 1.02)	.47	0.97 (0.95 to 1.00)	.03	0.98 (0.95 to 1.00)	.10
Breast volume per 100 mL, centered at 1,150 mL, continuous	1.03 (1.01 to 1.05)	.002	1.04 (1.02 to 1.06)	< .001	1.00 (0.99 to 1.02)	.39
Institution-level variable/level						
Teaching institution						
Yes *v* No	0.74 (0.59 to 0.93)	.009	0.84 (0.68 to 1.04)	.11	0.98 (0.81 to 1.19)	.85

Abbreviations: BMI, body mass index; OR, odds ratio.

[a]For factors with more than two levels, the overall, group *P* value is reported together with pairwise *P* values for each level of the factor compared with the reference level.

[b]Group *P* value.

TABLE A2. Multilevel Multivariable Models Explaining Toxicities for the Conventionally Fractionated Cases, With Patients Clustered Within Institution

	Moderate to Severe Breast Pain		Frequent Bother		Severe Fatigue	
Variable/Level	**OR (95% CI)**	***P*[a]**	**OR (95% CI)**	***P*[a]**	**OR (95% CI)**	***P*[a]**
Patient-level variables/level						
Age group, years		< .001[b]		< .001[b]		< .001[b]
< 50	2.02 (1.72 to 2.38)	< .001	2.18 (1.85 to 2.57)	< .001	1.51 (1.19 to 1.92)	< .001
50-59	1.63 (1.44 to 1.84)	< .001	1.71 (1.45 to 2.01)	< .001	1.35 (1.12 to 1.62)	.002
60-69 (referent)	1		1		1	
≥ 70	0.89 (0.77 to 1.03)	.12	0.72 (0.60 to 0.88)	.001	0.86 (0.68 to 1.08)	.19
BMI category, kg/m^2		.003[b]		.85[b]		.017[b]
Underweight, < 18.5	0.93 (0.60 to 1.44)	.75	1.16 (0.77 to 1.75)	.46	1.19 (0.82 to 1.72)	.36
Normal, 18.5 to < 25	0.83 (0.66 to 1.05)	.11	1.03 (0.80 to 1.33)	.82	0.79 (0.60 to 1.05)	.11
Overweight, 25 to < 30 (referent)	1		1		1	
Obesity I, 30 to < 35	1.14 (0.92 to 1.40)	.23	1.00 (0.83 to 1.22)	.98	1.21 (0.94 to 1.55)	.14
Obesity II, 35 to < 40	1.10 (0.88 to 1.38)	.40	0.91 (0.73 to 1.13)	.40	1.04 (0.79 to 1.37)	.78
Obesity III, > 40	1.51 (1.12 to 2.03)	.006	0.99 (0.69 to 1.42)	.95	1.00 (0.70 to 1.42)	.99
Race		< .001[b]		< .001[b]		.95[b]
White (referent)	1		1		1	
Black	2.04 (1.69 to 2.47)	< .001	1.35 (1.11 to 1.65)	.003	0.92 (0.65 to 1.30)	.62
Asian	1.44 (0.78 to 2.66)	.24	0.75 (0.46 to 1.21)	.24	0.98 (0.61 to 1.57)	.95
Other	2.16 (1.34 to 3.50)	.002	1.88 (1.23 to 2.87)	.004	1.04 (0.65 to 1.66)	.88
Hypertension						
Yes *v* No	0.89 (0.78 to 1.03)	.11	0.77 (0.69 to 0.87)	< .001	1.14 (0.96 to 1.34)	.13
Diabetes						
Yes *v* No	1.29 (1.11 to 1.50)	.001	1.36 (1.14 to 1.64)	< .001	1.35 (1.10 to 1.65)	.003
Smoking status		< .001[b]		< .001[b]		.006[b]
Never smoker (referent)	1		1		1	
Former smoker	1.19 (1.03 to 1.38)	.02	1.28 (1.14 to 1.44)	< .001	1.12 (0.93 to 1.36)	.23
Current smoker	1.58 (1.30 to 1.91)	< .001	1.65 (1.32 to 2.07)	< .001	1.45 (1.16 to 1.83)	.001
Chemotherapy						
Yes *v* No	0.85 (0.72 to 1.02)	.08	0.78 (0.65 to 0.93)	.007	0.86 (0.74 to 1.00)	.05
Boost						
Yes *v* No	1.09 (0.83 to 1.43)	.53	1.08 (0.83 to 1.42)	.56	0.82 (0.61 to 1.09)	.17
Separation distance, centered at 22 cm, continuous	1.02 (0.98 to 1.06)	.35	1.03 (1.01 to 1.06)	.01	1.04 (1.01 to 1.07)	.01
Breast volume per 100 mL, centered at 1,150 mL, continuous	1.03 (1.02 to 1.04)	< .001	1.04 (1.02 to 1.06)	< .001	1.00 (0.99 to 1.01)	.66
Supraclavicular field						
Yes *v* No	1.06 (0.89 to 1.27)	.52	1.17 (1.04 to 1.30)	.006	0.84 (0.70 to 1.01)	.06
Institution-level variable/level						
Teaching institution						
Yes *v* No	0.91 (0.65 to 1.28)	.60	0.97 (0.72 to 1.31)	.86	1.02 (0.87 to 1.20)	.82

Abbreviations: BMI, body mass index; OR, odds ratio.

[a]For factors with more than two levels, the overall, group *P* value is reported together with pairwise *P* values for each level of the factor compared with the reference level.

[b]Group *P* value.