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BRIEF REPORT

Are We Missing Acute Toxicities Associated With Hypofractionated Breast Irradiation? A Report From a Large Multicenter Cohort Study

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Purpose: The efficacy and long-term safety of hypofractionated whole breast irradiation (HF-WBI) have been established through multiple randomized trials, yet data about acute toxicities remain more limited. Since 2013, our group has prospectively collected acute toxicity data from weekly treatment evaluations and additional assessment after completion. In 2016, we intentionally shifted the posttreatment assessment follow-up visit from 1 month to 2 weeks to evaluate for missed acute toxicity occurring in that immediate posttreatment window. Here, we report whether 2-week follow-up has resulted in increased detection of acute toxicities compared with 4-week follow-up.

Methods and Materials: We prospectively compared acute toxicity for patients treated with HF-WBI between January 1, 2013, and August 31, 2015 (4 week follow-up cohort) to patients treated between January 1, 2016, and August 31, 2018 (2 week follow-up cohort). Analyses included a multivariable model that adjusted for other factors known to correlate with toxicity. We prospectively defined acute toxicity as maximum breast pain (moderate or severe rating) and/or occurrence of moist desquamation reported 7 days before the completion of radiation therapy (RT) until 42 days after completion.

Results: A total of 2689 patients who received postlumpectomy radiation and boost were analyzed; 1862 patients in the 2-week follow-up cohort and 827 in the 4-week follow-up cohort. All acute toxicity measures assessed were statistically similar between follow-up cohorts when compared in an unadjusted fashion. Overall acute composite toxicity was 26.4% and 27.7% for patients in the 4-week follow-up and 2-week follow-up cohorts, respectively. Overall acute composite toxicity remained similar between follow-up cohorts in a multivariable, adjusted model and was significantly related to patient's age, body mass index, smoking status, and treatment technique (intensity-modulated RT vs 3-dimensional conformal radiation therapy) but not follow-up cohort.

Conclusions: An earlier posttreatment follow-up for HF-WBI patients did not reveal a significant increased incidence of acute toxicities at 2 weeks compared with 4 weeks. This study provides physicians and patients with additional data on the safety and tolerability of HF-WBI for early stage breast cancer.

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Introduction

Whole breast irradiation (WBI) is the most prescribed radiation therapy (RT) for the treatment of early stage breast cancer in the United States. Moderately hypofractionated (HF-WBI) regimens (total doses of 4000 or 4250 cGy delivered daily over 15 or 16 days, respectively) have been shown through multiple phase III randomized trials[1-3] to provide similar disease control and patient survival compared with conventionally fractionated (CF-WBI; total doses of 4500 or 5000 cGy delivered daily over 25 days) regimens, regardless if treatment includes or excludes a sequential tumor bed boost. Additionally, multiple randomized trials have shown that late treatment-related toxicities with HF-WBI are comparable or decreased versus CF-WBI regimens. The American Society for Radiation Oncology updated its guidelines for WBI fractionation use in 2018,[4,5] stating that high quality data exist to suggest that in women undergoing WBI with or without inclusion of the low axillary lymph nodes (level 1), the preferred RT regimen is an HF course.

However, there remains a knowledge gap in the published literature regarding the characterization of acute toxicities associated with HF-WBI. Patients are routinely evaluated for toxicity while on treatment and then at 1 month posttreatment or later. It is unknown if acute toxicity has been adequately assessed (both on clinical trials and as reported in retrospective series[1,2,3,6]) given this frequency of observation. Many have wondered if acute toxicity could be underreported if the maximum toxicity evolves within the interval between final treatment and 1 month follow-up, especially for hypofractionated regimens.

The Michigan Radiation Oncology Quality Consortium (MROQC) is a quality improvement initiative that includes 26 practices across the state. It is funded by Blue Cross Blue Shield of Michigan and has been described in detail.[6,7] One of its missions is to identify ways to improve breast cancer treatments by reducing radiation-associated toxicity. Patient demographics, disease characteristics, RT treatment parameters, and clinical toxicity outcomes for all women receiving WBI as part of breast conserving therapy are data points collected and recorded by MROQC. In this paper, we report on prospectively collected acute toxicity data for the HF-WBI population designed to address whether an earlier posttreatment clinical assessment may detect otherwise unobserved acute toxicities.

Methods and Materials

From 2011 to 2015, centers prospectively collected acute toxicity data during weekly on-treatment evaluations and 1 month after completion of RT. This represented the most popular practice patterns among the diverse group of clinicians participating in MROQC during this time period. After publication of the consortium's data suggested significantly less acute toxicity for HF-WBI patients compared with CF-WBI,[8] a concern was raised by consortium members regarding whether acute skin toxicity (moist desquamation and breast pain) was present but not reported among HF-WBI patients because of the shorter length of therapy and the gap in follow-up between the end of treatment and the standard 1-month follow-up. To address this, the consortium modified the timing of clinical follow-up to replace the 1-month follow-up with a 2-week post-RT completion visit in late 2015.

To assess the effect of this new evaluation timepoint, we reviewed all HF-WBI cases completing RT between January 1, 2013, and August 31, 2018. We compared patients during 2 separate 3-year periods: those treated between January 1, 2013, and August 31, 2015 (before 2-week follow-up was adopted, the 4 week follow-up cohort) and patients treated between January 1, 2016, and August 31, 2018 (after adoption of a 2-week follow-up, the 2 week follow-up cohort).

Toxicity assessments were routinely collected weekly during ongoing radiation treatment, during the last week of treatment, and during follow-up visits. We prospectively defined acute toxicity as maximum breast pain reaching a moderate or severe level and/or the occurrence of moist desquamation reported 7 days before the completion of RT until 42 days (6-weeks) after completion. Breast pain was measured by the patient using a modification of the Brief Pain Inventory (0-10) scale, with moderate/severe breast pain defined as a score of 4 to 10. When patient ratings were absent, we substituted physician-assessed breast pain using the Common Terminology Criteria for Adverse Events version 4.0 grading schema, with values of 2 to 4 indicating at least moderate breast pain. Physicians assessed the presence/absence of moist desquamation.

For analysis, patients were required to have at least 1 toxicity assessment by a treating physician within the interval of 7 days before to 42 days after the completion of RT, considered a valid assessment for the 4-week cohort. When multiple assessments of toxicity occurred, the maximum toxicity over the period was used. For the 2-week cohort the same period assessment was used, though that cohort was more likely to have a valid 2-week assessment, which was defined as having occurred between 7 and 21 days after completing RT. Cases were limited to those treated in the supine position, without directed nodal fields, receiving a tumor bed boost, and with separation values of 15 cm or larger. Prescriptions for whole breast treatment and the tumor bed boost were at the discretion of the treating radiation oncologist.

We compared characteristics between follow-up cohorts using the χ^2 test and the 2-sample test for categorical and continuous data, respectively. We calculated rates of acute toxicities for both follow-up cohorts. We constructed multiple variable logistic regression models to compare between periods in an adjusted fashion. Adjustment covariates

Table 1 Sample description

Variable	Level	4-wk follow-up cohort	2-wk follow-up cohort	P*
Age: Mean (SD)	Continuous	63.1 (10.2)	62.3 (10.1)	.06
Age groups: No. (%)	Age ≤ 50	81 (9.8)	219 (11.8)	.36
	50 < age ≤ 60	246 (29.8)	549 (29.5)	
	60 < age ≤ 70	295 (35.7)	673 (36.1)	
	70 < age	205 (24.8)	421 (22.6)	
Race: No. (%)	White	637 (77.0)	1495 (80.3)	.02
	Black	144 (17.4)	272 (14.6)	
	Asian	11 (1.3)	42 (2.3)	
	Other	35 (4.2)	53 (2.9)	
Separation: Mean (SD)	Continuous	22.2 (3.4)	22.7 (3.5)	<.001
Separation > 25 cm: No. (%)	No	680 (82.2)	1424 (76.5)	<.001
	Yes	147 (17.8)	438 (23.5)	
Breast volume (cc): Mean (SD)	Continuous	960 (530)	1082 (653)	<.001
BMI: Mean (SD)	Continuous	29.1 (6.5)	29.6 (6.5)	.13
BMI categories: No. (%)	Underweight <18.5	12 (1.5)	26 (1.4)	.47
	Normal 18.5 to <25	230 (27.8)	477 (25.6)	
	Overweight 25 to <30	271 (32.8)	613 (32.9)	
	Obesity I 30 to <35	177 (21.4)	412 (22.1)	
	Obesity II 35 to <40	91 (11.0)	194 (10.4)	
	Obesity III >40	46 (5.6)	140 (7.5)	
Smoking status: No. (%)	Never smoker	439 (53.1)	1084 (58.2)	.046
	Former smoker	284 (34.3)	568 (30.5)	
	Current smoker	104 (12.6)	210 (11.3)	
At least 1 comorbidity†: No. (%)	No	407 (49.2)	935 (50.2)	.63
	Yes	420 (50.8)	927 (49.8)	
Breast cancer disease stage: No. (%)	Not reportable	3 (0.4)	4 (0.2)	.69
	0	178 (21.5)	417 (22.4)	
	1	504 (60.9)	1098 (59.0)	
	2	141 (17.1)	342 (18.4)	
	3	1 (0.1)	1 (0.1)	
Laterality: No. (%)	Left	377 (45.6)	899 (48.3)	.20
	Right	450 (54.4)	963 (51.7)	
Histology: No. (%)	IDC: predominant	561 (67.8)	1241 (66.7)	.93
	IDC other: less aggressive histology	19 (2.3)	47 (2.5)	
	ILC: predominant	67 (8.1)	144 (7.7)	
	DCIS	179 (21.6)	417 (22.4)	
	Missing/other	1 (0.1)	13 (0.7)	
Estrogen receptor: No. (%)	Not reported	5 (0.6)	9 (0.5)	.95
	Negative	108 (13.1)	245 (13.2)	
	Positive	714 (86.3)	1608 (86.4)	

(*Continued*)

Table 1 (*Continued*)

Variable	Level	4-wk follow-up cohort	2-wk follow-up cohort	*P*[*]
Progesterone receptor: No. (%)	Not reported	9 (1.1)	32 (1.7)	.76
	Negative	167 (20.2)	383 (20.6)	
	Positive	651 (78.7)	1447 (77.7)	
Chemotherapy: No. (%)	Not reported	7 (0.9)	10 (0.5)	.75
	No	680 (82.2)	1545 (83.0)	
	Yes	140 (16.9)	307 (16.5)	
Mean dose delivered to the breast: Mean (SD)	Continuous	46.58 (2.3)	46.08 (1.9)	<.001
Whole breast prescription: No. (%)	4000 cGy, 15-16 fractions	67 (8.1)	287 (15.4)	—
	4125 cGy, 15 fractions	32 (3.9)	0	
	4200-4300 cGy, 16 fractions	701 (84.8)	1543 (82.9)	
	Other	27 (3.2)	32 (1.7)	
Surgical bed boost prescription: No. (%)	795 cGy, 15 fractions (concurrent)	27 (3.3)	0	—
	900 cGy, 5 fractions	31 (3.7)	2 (0.1)	
	1000 cGy, 4 fractions	201 (24.3)	983 (52.8)	
	1000 cGy, 5 fractions	248 (30.0)	581 (31.2)	
	1064 cGy, 4 fractions	55 (6.7)	183 (9.8)	
	1200 cGy, 6 fractions	172 (20.8)	22 (1.2)	
	1250 cGy, 5 fractions	13 (1.6)	20 (1.1)	
	1400 cGy, 7 fractions	24 (2.9)	9 (0.5)	
	1600 cGy, 8 fractions	21 (2.5)	9 (0.5)	
	Other	35 (4.2)	53 (2.8)	
Treatment technique: No. (%)	Not reported	4 (0.48)	1 (0.05)	<.001
	3DCRT	504 (60.9)	972 (52.2)	
	IMRT	319 (38.6)	889 (47.7)	

Abbreviations: 3DCRT = 3 dimensional conformal radiation therapy; BMI = body mass index; DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; IMRT = intensity modulated radiation therapy.

[*] Two-group *t* test for continuous data and the χ^2 test for categorical data comparing between treatment cohorts; missing or not reported categories ignored.

[†] Presence of at least 1 comorbidity thought to increase the likelihood of skin toxicity/breast pain: hypertension, diabetes, scleroderma, rheumatoid arthritis, lupus, connective tissue disorder, or peripheral vascular disease.

included age, body mass index (BMI), breast volume (cc), patient race (White, Black, Asian, other), presence of at least 1 comorbidity thought to increase the likelihood of skin toxicity/pain (hypertension, diabetes, scleroderma, rheumatoid arthritis, lupus, connective tissue disorder, or peripheral vascular disease), smoking status, and RT delivery type (3 dimensional conformal radiation therapy [3DCRT] vs intensity modulated RT [IMRT], with IMRT defined as any treatment beam delivered with 5 or more segments). All statistical analyses were completed using the SAS System, 9.4.

Results

A total of 2689 patients who received postlumpectomy WBI were analyzed; 1862 patients in the 2-week follow-up cohort and 827 in the 4-week follow-up cohort. Patients were similar between the 4-week and 2-week follow-up cohorts for patient age, BMI, presence of important comorbidities, breast cancer group stage, disease histology, laterality of affected breast, receptor status (ER and PR), and chemotherapy use (Table 1). Patients in the 2-week follow-up cohort were more likely to have a larger breast volume (mean, 1082 vs 960 cc; $P < .0001$), larger separation distance (mean, 22.7 vs 22.2 cm; $P = .0009$), to be treated by an IMRT technique (47.7% vs 38.6%; $P < .0001$), and to be White (80.3% vs 77.0%; $P = .0230$). Patients in the 2-week follow-up cohort were less likely to be current or former smokers (41.8% vs 46.9%; $P = .0462$). Mean radiation dose delivered to the breast (WBI and surgical bed boost) was significantly but only slightly higher during the 4-week versus the 2-week follow-up cohort (mean SD, 4658 [226] vs 4608

Table 2 Acute toxicity [−7, 42 days] after date of last fraction

Variable	Level	4-wk follow-up cohort	2-wk follow-up cohort	P*
Physician assessed				
CTCAE breast pain: No. (%)	Not reported	48 (5.8)	100 (5.4)	.08
	0	345 (41.7)	685 (36.8)	
	1	376 (45.5)	924 (49.6)	
	2	54 (6.5)	144 (7.7)	
	3	4 (0.5)	9 (0.5)	
Moist desquamation: No. (%)	Not reported	36 (4.4)	85 (4.6)	.08
	Absent	709 (85.7)	1631 (87.6)	
	Present	82 (9.9)	146 (7.8)	
Patient assessed				
Pain rating at maximum, categories: No. (%)	Not reported	13 (2.1)	55 (3.9)	.48
	0 None	172 (27.4)	351 (24.8)	
	1-3 Mild	294 (46.8)	643 (45.4)	
	4-7 Moderate	105 (16.7)	247 (17.4)	
	8-10 Severe	44 (7.0)	120 (8.5)	
Composite of physician- and patient-assessed toxicity				
Overall composite toxicity†: No. (%)	Not reported	25 (3.0)	34 (1.8)	.60
	No	584 (70.6)	1313 (70.5)	
	Yes	218 (26.4)	515 (27.7)	

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.
* Chi-square test for categorical data comparing between treatment cohorts, missing or not reported categories ignored.
† Moderate-to-severe breast pain as assessed by patient or physician and/or physician-assessed moist desquamation.

[192] cGy, respectively). The most common whole breast treatment prescription was between 4200 and 4300 cGy delivered in 16 fractions, used for 84.8% and 82.9% of cases in the 4-week and 2-week follow-up cohort, respectively. The most common surgical bed boost prescription was between 1000 and 1064 cGy delivered in 4 or 5 fractions, used for 61% and 93.8% of cases in the 4-week and 2-week follow-up cohort, respectively. Prescriptions for the whole breast or the surgical bed representing greater than 1% of cases in either cohort are reported in Table 2.

Overall composite acute toxicity was defined as patient self-reported moderate/severe breast pain and/or Common Terminology Criteria for Adverse Events physician-graded breast pain 2+ or physician-identified moist desquamation (Table 2). All acute toxicity measures assessed were statistically similar between follow-up cohorts when compared in an unadjusted fashion. Overall composite toxicity was reported for 26.4% of patients during the 4-week follow-up cohort and for 27.7% during the 2-week follow-up cohort. Finally, when comparing the overall composite acute toxicity in multivariable, adjusted models, there remained no statistical difference between follow-up cohorts (Fig. 1). Overall composite toxicity was significantly related to patient age, with older patients less likely to have toxicity. If we consider continuous age, along with all the remaining adjustment covariates, the estimated odds ratio for a 1-year increase in age was 0.966 (95% CI, 0.956-0.975; $P < .0001$); BMI, patients with a higher index more likely to have toxicity; smoking status, both former and current smokers more like to have toxicity than never smokers; and treatment technique, patients treated with IMRT less likely to have toxicity than patients treated with 3DCRT.

Discussion

This large multicenter quality consortium prospectively collected data on physician- and patient-assessed acute toxicities during the course of RT for HF-WBI patients, permitting evaluation of whether the addition of a short-interval follow-up visit detected previously undetected toxicity. We found that a closer posttreatment follow-up did not reveal evidence of increased treatment moderate to severe breast pain and/or moist desquamation in this very large patient cohort.

The prospective nature of data collection, the large number of patients and radiation oncology centers represented, and the use of both physician- and patient-assessed toxicity measures are strengths of this study. The findings herein are

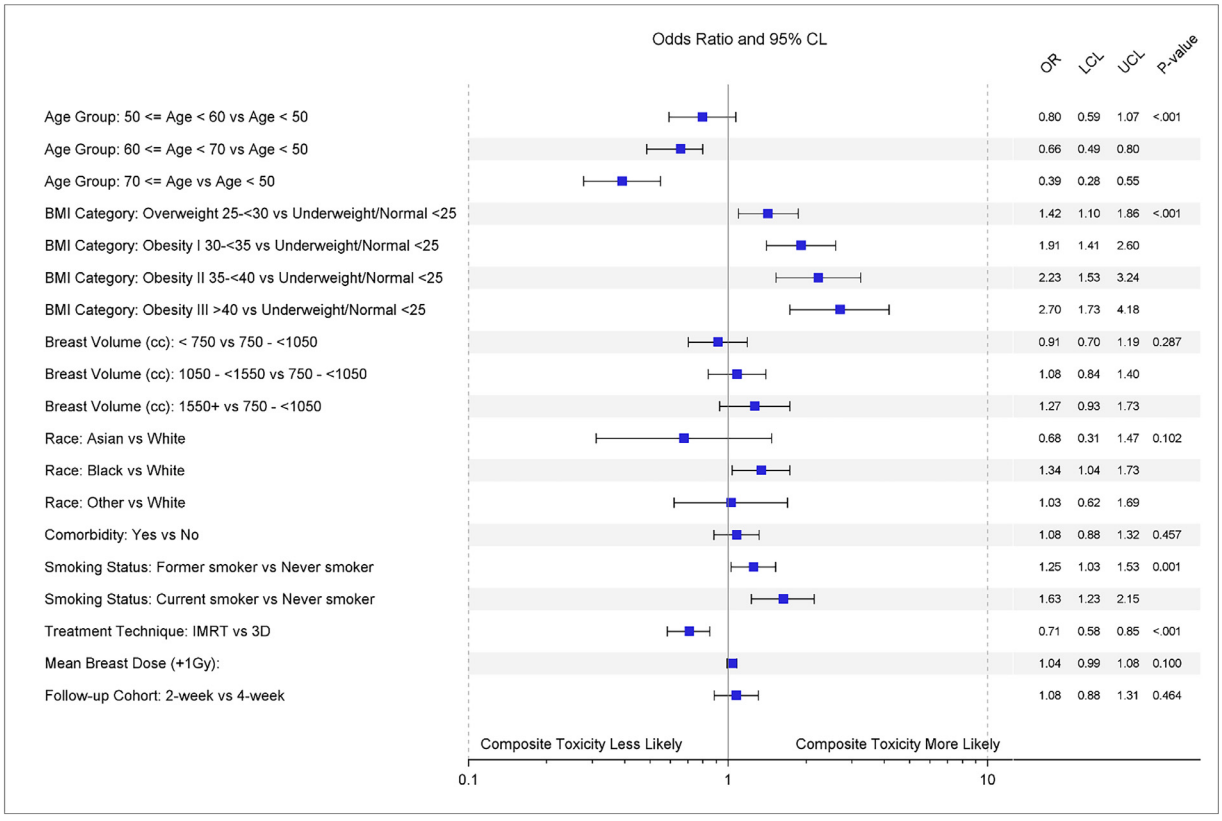

Fig. 1. Multiple variable logistic regression model explaining overall composite toxicity.

consistent with previously reported data from randomized trials and other retrospective data[1,2,3,8,9] but go beyond existing evidence to answer an important, previously unsettled question - whether toxicity rates would be higher if assessed earlier after the completion of HF-WBI.

Study limitations include the possibility of selection bias affecting this observational analysis because of the nonrandom allocation to follow-up timing based on a change for all patients treated in a particular period. The 2-week follow-up cohort included more patients, likely because of the more liberal use of moderate hypofractionation over time, and this is reflected in limited differences in the distribution of characteristics between cohorts, with the HF-WBI cohort including patients with larger separation and larger breast volumes.

Of note, there were some significant differences in overall composite toxicity regardless of follow-up timepoint. Patients treated with IMRT were less likely to have toxicity than patients treated with 3DCRT, as expected and previously reported.[9] Patients with a higher BMI were more likely to have toxicity. This is also expected given higher beam entry and exit dose-max and the possibility of excess electron scatter with increasing skin redundancy. Of interest, however, both former and current smokers were more likely to have toxicity than never-smokers and older patients were less likely to have toxicity than younger patients. In fact, if we consider continuous age, along with all the remaining adjustment covariates, the odds of having toxicity (composite toxicity: breast pain or moist desquamation) decreases by 3.4% for each year increase in age of the patient at time of RT.

Conclusion

An earlier posttreatment follow-up for patients receiving HF-WBI did not reveal an increased incidence of acute toxicities when scheduled routinely at 2 weeks compared with 4 weeks. This study provides physicians and patients with additional data on the safety and tolerability of HF-WBI in early-stage disease as they relate to short-term follow-up.

Factors predicting a decreased risk of acute dermatitis included use of IMRT, lower BMI, never-smoker status, and older age.

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