original contributions

Racial Differences in Treatments and Toxicity in Patients With Non–Small-Cell Lung Cancer Treated With Thoracic Radiation Therapy

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QUESTION ASKED: Given historical differences in surgery rates and survival in Black patients diagnosed with lung cancer, what racial differences in thoracic radiation treatments and toxicities exist in patients with non–small-cell lung cancer undergoing definitive treatment?

SUMMARY ANSWER: This large multi-institutional study found no evidence of racial differences in radiation treatment or chemotherapy approaches. However, the lower odds of provider-reported pneumonitis and weaker correlation between swallowing symptoms and esophagitis in Black patients are suggestive of under-recognition of treatment-related toxicities in Black patients, and further research is warranted.

WHAT WE DID: A large statewide patient-level database of patients with lung cancer who received definitive thoracic radiation was analyzed to assess associations between race, treatment variables, patient-reported symptoms, and provider-reported toxicity.

WHAT WE FOUND: Race was not significantly associated with radiation or chemotherapy approach. However, there were significant differences by race with respect to patient-reported pain (significantly higher in Black patients at two time points) and provider-reported pneumonitis (significantly lower in Black patients, even after controlling for known patient and treatment factors; odds ratio 0.36, $P = .03$).

BIAS, CONFOUNDING FACTORS, REAL-LIFE IMPLICATION: Several limitations of this study include inability to determine causality because of the observational nature of the data. Furthermore, certain contributing factors were not measured such as provider demographics, communication styles, and patient-level social determinants of health including education level and insurance status that may have contributed to the findings observed. This study is also geographically restricted to the state of Michigan and is not necessarily representative of racial differences that may be observed in other geographic regions.

REAL-LIFE IMPLICATIONS: The most encouraging finding from this study was the lack of significant differences by race in terms of radiation and chemotherapy treatment patterns. This represents encouraging progress from a historical era during which lower rates of surgery in Black patients with lung cancer resulted in lower rates of survival. However, the findings from this study that warrant further research include possible under-recognition of Black patients' symptoms, particularly with regards to treatment-related esophagitis. This study's findings offer important insight into the care of racially diverse patients. For practicing oncologists, care should be taken to ensure that each patient's symptoms are recognized and supported during and after oncologic treatments. Further investigation into the social determinants of health beyond race that may have contributed to the findings observed is needed.

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Data Supplement

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EQUITY IN CANCER CARE

original contributions

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abstract

PURPOSE Historical racial disparities in lung cancer surgery rates resulted in lower survival in Black patients. Our objective was to examine racial differences in thoracic radiation treatments and toxicities in patients with non–small-cell lung cancer.

METHODS AND MATERIALS A large institutional review board–approved statewide patient-level database of patients with stage II-III non–small-cell lung cancer who received definitive thoracic radiation from March 2012 to November 2019 was analyzed to assess associations between race and other variables. Race (White or Black) was defined by patient self-report. Provider-reported toxicity was defined by Common Terminology Criteria for Adverse Events version 4.0. Patient-reported toxicity was determined by the Functional Assessment of Cancer Therapy–Lung quality-of-life instrument. Univariable and multivariable regression models were fitted to assess relationships between race and variables of interest. Spearman rank-correlation coefficients were calculated between provider-reported toxicity and similar patient-reported outcomes.

RESULTS One thousand four hundred forty-one patients from 24 institutions with mean age 68 years (range, 38-94 years) were evaluated. Race was not significantly associated with radiation or chemotherapy approach. There was significantly increased patient-reported general pain in Black patients at the preradiation and end-of-radiation time points. Black patients were significantly less likely to have provider-reported grade 2+ pneumonitis (odds ratio 0.36, $P = .03$), even after controlling for known patient and treatment factors. Correlation coefficients between provider- and patient-reported toxicities were generally similar across race groups except for a stronger correlation between patient- and provider-reported esophagitis in White patients.

CONCLUSION In this large multi-institutional study, we found no evidence of racial differences in radiation treatment or chemotherapy approaches. We did, however, unexpectedly find that Black race was associated with lower odds of provider-reported grade 2+ radiation pneumonitis. The stronger correlation between patient- and provider-reported esophagitis and swallowing symptoms for White patients also suggests possible under-recognition of symptoms in Black patients. Further research is needed to study the implications for Black patients.

INTRODUCTION

Historically, patients with non–small-cell lung cancer (NSCLC) of different race and ethnicity backgrounds underwent different rates of definitive cancer treatments such as surgery, and this contributed to higher observed lung cancer–specific mortality in patients of color. For example, a study conducted in the 1980s to 1990s found that the rate of surgery was 13% lower for Black patients than White patients, and subsequently a lower 5-year survival rate was observed in Black patients (26%, *v* 34% in Whites).[1] However, among patients who received similar surgical treatment for their early-stage lung cancer, the survival rates were similar.[1] This study highlights the importance of ensuring equal access to high-quality cancer treatments for patients of all races. This is particularly important given the continuation of racial disparities in lung cancer into the modern era. Blom et al[2] analyzed a large cohort of National Cancer Database patients to determine the association of patient variables with guideline-concordant treatment patterns and found that elderly (age ≥ 80 years) and non-Hispanic Black patients were less likely to receive guideline-concordant treatment for lung cancer.

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Contemporary recommended treatments for lung cancer include a variety of multimodality approaches involving surgery or radiation therapy (RT) for earlier stages and often a combination of chemotherapy and radiation (sometimes with surgery or immunotherapy) for later stages of disease.[3,4] With the breadth of treatment modalities now available, it is critical to ensure similar access to guideline-concordant, high-quality cancer care for every patient regardless of race. The modern era has also heralded the significance of including patient-reported outcomes (PROs) as a metric that contributes to the patient's narrative of their cancer illness journey.[5] Therefore, we have previously endeavored to examine both patient- and provider-reported toxicities and to compare the correlation between those metrics in our study population.[6] In this study, we aimed to observe whether any differences exist by race (Black or White) in a large multi-institutional statewide consortium of patients receiving RT for stage II-III lung cancer in terms of state-wide treatment patterns, treatment toxicities, and clinician recognition of treatment toxicities reported by patients.

METHODS AND MATERIALS

This analysis included patients who received definitive thoracic RT for American Joint Committee on Cancer 7th edition stage II-III NSCLC lung cancer from March 2012 through November 2019. This study was institutional review board (IRB)–approved as a collaborative quality initiative with voluntary patient participation in surveys, and clinical assessment and treatment information on all eligible patients entered into the quality consortium database. Patients with stage I and stage IV lung cancer were not included in this study because we were specifically examining treatments and toxicities in patients receiving definitive treatment for locally advanced lung cancer and we restricted our study to stage II-III. Patient information was collected prospectively as part of a statewide consortium, Michigan Radiation Oncology Quality Consortium (MROQC). This study was a retrospective review of this prospectively gathered database. MROQC is a multicenter statewide collaboration that is funded by Blue Cross and Blue Shield of Michigan and Blue Care Network to collect clinical, sociodemographic, treatment, dosimetric, and outcome data for patients receiving RT in Michigan.[7] Data are collected on all eligible patients in MROQC practices, regardless of their insurance type, and MROQC includes patients from all insurers, and not just plans within Blue Cross and Blue Shield of Michigan. All data analyses were performed independently of the funding organization. Periodic internal audits are performed of MROQC data for review of data integrity. For this analysis, data from 24 academic and community clinics were available.

Information in the MROQC databases includes patient demographics, tumor stage, location, histology, and treatment information including treatment plans, dose-volume histograms, and use of chemotherapy. Each institution also provides prescription dose, separate from the dose-volume histogram data.[8] Race was defined by patient self-report. If racial data by self-report were not available, this information was recorded from available medical records. During radiation treatment, patients were evaluated on a weekly basis by the treating radiation oncologist. Follow-up continued by the treating radiation oncologist for 1-, 3-, and 6-month visits after the conclusion of RT. Additionally, the Charlson Comorbidity Index was referenced in our study for defining which medical comorbidities to include and report.

Before beginning RT, patients also completed the Physical Well-Being, Functional Well-Being, and Lung Cancer Symptoms subscales of the Functional Assessment of Cancer Therapy–Lung quality-of-life instrument.[9] In the Functional Assessment of Cancer Therapy–Lung, patients rate the extent to which they were bothered by 22 unique symptoms in the past 7 days. Patient bother is rated as not at all (0), a little bit (1), somewhat (2), quite a bit (3), or very much (4). Patient-reported trouble swallowing was also rated on a 5-point scale both weekly during RT and at follow-up visits, with the following scores: no trouble (0), mild soreness only (1), can swallow solids with some difficulty (2), cannot swallow solids (3), and cannot swallow liquids (4). The basis for the provider-reported toxicity grading was the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

IRB/Consent

The Office for Human Research Protections (OHRP) Quality Improvement (QI) Activities Frequently Asked Questions states "Most QI efforts are not research subject to the U.S. Department of Health and Human Services (HHS) protection of human services regulations."[10] MROQC is designed for the purpose of QI, and the QI initiatives supported by MROQC are not designed to accomplish a research purpose (such as introducing an untested clinical intervention to establish scientific evidence). The MROQC Coordinating Center, in consultation with the University of Michigan Health System Legal Office, believes that the work of the collaborative does not satisfy the definition of research; therefore, the HHS regulations for the protection of human subjects do not apply, and there is no requirement under the regulations for IRB oversight. Additionally, the University of Michigan Medical School IRB, which is registered with the OHRP, has reviewed the work of the collaborative and made a determination that it is not regulated. The following comes from the OHRP QI Frequently Asked Questions and is relevant to the MROQC quality initiatives:

Do QI activities fall under the HHS regulations for the protection of human subjects in research (45 CFR part 46) if their purposes are limited to (1) delivering health care and (2) measuring and reporting provider performance data for clinical, practical, or administrative uses?

No, such QI activities do not satisfy the definition of research under 45 CFR 46.102(d), which is a systematic

investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Therefore, the HHS regulations for the protection of human subjects do not apply to such QI activities, and there is no requirement under these regulations for such activities to undergo review by an IRB, or for these activities to be conducted with provider or patient informed consent.

The clinical, practical, or administrative uses for such performance measurements and reporting could include, for example, helping the public make more informed choices regarding health care providers by communicating data regarding physician-specific surgical recovery data or infection rates. Other practical or administrative uses of such data might be to enable insurance companies or health maintenance organizations to make higher performing sites preferred providers, or to allow other third parties to create incentives rewarding better performance.

Data Collection

The specific data collection for MROQC involves medical record review covering the medical and oncology history and treatment as well as physics data related to the individual's radiation treatment. This is necessary for the QI activities to assess whether certain treatments and/or outcomes are affected by changes in practice made as a result of the use of the data collection and QI strategies. Patients will be asked to both join MROQC and to participate in patient surveys. Patients will be informed during a preradiation treatment visit about the initiative and will be given the opportunity to refuse to respond to any questions. This request is considered similar to patient contact for satisfaction surveys or similar QI activities.

Statistical Methods

Generalized linear mixed-effects models were fit to assess the association between race and treatment variables (intensity-modulated RT [IMRT], concurrent chemotherapy, and RT dose) while adjusting for relevant disease characteristics, such as disease stage and the number of structures (including the esophagus, heart, great vessels, spinal cord, and brachial plexus) within 2 cm of the planning target volume (PTV). These variables were selected a priori as clinical and dosimetric variables that may be associated with toxicity. For example, structures within 2 cm of the primary tumor may be more likely to receive a higher dose and thus at increased risk of acute toxicities relative to structures further from the tumor. Covariates including the PTV and highest dose to 2 cc of volume (D2cc) to the esophagus were centered and scaled, which involved the process of subtracting the mean value from the recorded value and then dividing by the standard deviation. The metric D2cc to the esophagus has been previously identified by our group as a dosimetric predictor of acute esophagitis in patients with lung cancer undergoing thoracic radiation.[11] To account for intrapatient correlations, a random intercept was used to allow for positive and fixed correlation between each pair of observations within a patient and this assumes independence between patients. Logistic regression models were used to characterize the association between race and binary toxicities (eg, grade 2 or higher pneumonitis and esophagitis) or patient-reported outcomes while adjusting for patient, treatment, and disease factors, and t-tests were used to evaluate for differences in proportions by race. A random intercept at the hospital level was included to account for center-level differences in practice patterns or patients who are not otherwise captured by the included covariates. To aid in model convergence, centers treating 15 or fewer patients were collapsed into a single category. Pneumonitis was defined as any occurrence of CTCAE grade 2+ toxicity, at any point during follow-up (up to 6 months). There were four specific time points evaluated including (1) end of radiation treatment, (2) 1 month post-RT, (3) 3 months post-RT, and (4) 6 months post-RT. Because some patients only had pneumonitis assessed at one or two time points post-RT, we calculated patient weights, such that patients who had available data at only one or two follow-up times were downweighed in comparison to patients seen at all three follow-up times. Weights were based on the relative frequency of grade 2+ pneumonitis at each time point and were normalized to sum to 1. Patients with full follow-up or observed toxicity were assigned a weight of 1. As an example, a patient who was missing two time points of data, but had pneumonitis grade 2+ at one of the observed time points, would receive full weight in our analysis. By contrast, a patient who never received a pneumonitis grade 2+ diagnosis but was only observed at the end of treatment and at a 1-month follow-up would receive a weight of 0.25, according to our weighting scheme. PROs were also dichotomized as a bother score of 3 (quite a bit or cannot swallow solids) or higher in response to their bother for six symptoms, at three different time points. For the symptom of general pain, a generalized linear mixed-effects model was created to evaluate the effect of time and race on the incidence of severe general pain while accounting for within-patient correlation. The fixed effect predictors included in the model are time (categorical covariate) and race group with an interaction term. A patient-level random intercept with no slope was included to account for the likely within patient correlation over time. Spearman rank-correlation coefficients were calculated to quantify the correlation between patient-reported symptom bother and provider-reported toxicities for the following symptom and toxicity combinations: patient-reported cough versus pneumonitis, patient-reported shortness of breath (SOB) versus pneumonitis, and patient-reported trouble swallowing versus esophagitis, and z-tests were used to evaluate for differences in correlations by race. All statistical analyses were performed using R software, version 4.0.0.[12]

RESULTS

Table 1 presents the demographic and treatment characteristics of the 1,441 patients with stage II-III NSCLC

TABLE 1. Demographic and Treatment Characteristics

Variable	Level	All Patients (N = 1,441)	White (n = 1,157)	Black (n = 226)	Other (n = 58)
Patient demographics					
Age, mean (SD), range, years	Continuous	68 (10.0), 38-99	68 (10.0), 38-99	67 (9.9), 41-90	66 (8.6), 47-84
Sex, No. (%)	Male	765 (53)	609 (53)	121 (54)	35 (60)
	Female	676 (47)	548 (47)	105 (46)	23 (40)
Smoking status, No. (%)	Current smoker	582 (40)	451 (39)	107 (48)	24 (42)
	Former smoker	785 (54)	643 (56)	111 (50)	31 (54)
	Never smoker	51 (4)	53 (5)	6 (2)	2 (4)
No. of comorbidities, mean (SD), range	Continuous	2 (1.5), 0-8	2 (1.5), 0-8	2 (1.5), 0-8	2 (1.3), 0-5
Stage, No. (%)	IIA	30 (3)	27 (2)	5 (2)	2 (3)
	IIB	150 (14)	123 (11)	34 (15)	7 (12)
	IIIA	623 (56)	546 (47)	100 (44)	26 (45)
	IIIB	306 (28)	268 (23)	48 (21)	14 (24)
PTV size, mean (SD), range, mL	Continuous	439 (333), 3.8-2,218.0	434 (327), 8.3-2,167	455 (345), 3.8-2,218	466 (406), 18.8-2,180
Treatment characteristics					
Chemotherapy, No. (%)	Concurrent	1,072 (74)	873 (75)	156 (69)	43 (74)
	Adjuvant	155 (11)	113 (10)	33 (15)	9 (16)
	Neoadjuvant	76 (5)	50 (4)	23 (10)	3 (5)
Radiation design, No. (%)	IMRT	928 (64)	747 (65)	136 (60)	45 (78)
	3DCRT	500 (35)	398 (35)	89 (40)	13 (22)
Mean lung dose, mean (SD), range, Gy	Continuous	14.7 (4.5), 0.11-69.1	14.7 (4.6), 0.16-69.1	14.9 (4.2), 0.11-26.2	14.8 (3.9), 3.7-23.0
D2cc to esophagus, mean (SD), range, Gy	Continuous	51.3 (15.7), 0.53-76.9	51.5 (15.4), 0.61-76.9	50.3 (17.0), 0.53-72.6	51.3 (14.2), 11.7-68.7
Mean heart dose, mean (SD), range, Gy	Continuous	12.5 (9.3), 0.05-58.0	12.4 (9.2), 0.11-58.0	12.0 (9.6), 0.05-45.0	15.0 (11.3), 0.86-54.9

Abbreviations: 3DCRT, three-dimensional conformal radiation therapy; D2cc, highest dose to 2 cc of volume; IMRT, intensity-modulated radiation therapy; PTV, planning target volume; SD, standard deviation.

treated with thoracic radiation from March 2012 to November 2019 who were enrolled in MROQC with racial categories of White (80%), Black (16%), and other (4%). The mean age for the overall cohort was 68 years (range, 38-99 years), and there was a fairly close split between male and female patients, 53% and 47%, respectively. The majority of patients were either current (40%) or former (54%) smokers, and the patients had two medical comorbidities on average (range 0-8). Although the proportion of smokers was numerically different between races, the difference was not statistically significant ($P > .05$). The majority of patients had stage III disease (56% stage IIIA and 28% stage IIIB). The PTV size was 439 mL on average. All baseline demographic characteristics were similar between White and Black patients.

In terms of treatment characteristics, as shown in Table 1, most patients (74%) received concurrent chemotherapy with thoracic radiation and with an IMRT treatment approach (64%). The mean lung dose was similar across racial groups, with average dose of 14.7 Gy. The D2cc to the esophagus and mean heart dose were also similar between racial groups with overall averages of 51.3 Gy and 12.5 Gy, respectively.

The Data Supplement (online only) shows the number of patients in each race category by hospital. Three institutions treated 61% of the Black patients in the overall cohort, nine treated 88%, and 12 of the 24 consortium institutions treated 91% of the Black patients with lung cancer.

Table 2 shows the hospital-adjusted logistic model results for treatment type and racial category. Race was not significantly associated with the odds of receiving concurrent, adjuvant, or neoadjuvant chemotherapy ($P = .76$), and stage was also not associated with the sequencing of chemotherapy ($P = .16$). Race was also not significantly associated with the odds of receiving IMRT versus three-dimensional conformal radiation therapy for thoracic RT ($P = .47$). However, patients with stage III (*v* II) NSCLC and those with a greater number of structures within 2 cm of the

TABLE 2. Logistic Models for Treatment Type

Treatment Model	Covariate	OR Estimate	95% CI	*P*
Model for treatment with concurrent chemotherapy	Black *v* White race	0.93	0.61 to 1.45	.76
	Stage III *v* II	1.30	0.89 to 1.86	.16
Model for treatment with IMRT	Black *v* White race	1.18	0.75 to 1.87	.47
	Stage III *v* II	1.78	1.19 to 2.65	**.005**
	No. of structures within 2 cm of PTV	1.36	1.14 to 1.64	**.0007**

NOTE. Bold entities indicate statistically significant and marginally significant findings.
Abbreviations: IMRT, intensity-modulated radiation therapy; OR, odds ratio; PTV, planning target volume.

PTV were significantly more likely to receive IMRT ($P = .005$ and $P = .0007$, respectively).

Table 3 shows the hospital-adjusted logistic model results for grade 2+ esophagitis and grade 2+ pneumonitis, where race is the key covariate of interest. Race, PTV size, and esophagus location within 2 cm of the PTV were not significantly associated with grade 2+ provider-reported esophagitis (*P* values of .16, .06, and .40, respectively); however, greater esophageal D2cc dose and use of concurrent chemotherapy with radiation were significantly associated with higher grade 2+ provider-reported esophagitis (*P* values of $< .0001$ and .01, respectively). In comparison, race was found to be significantly associated with grade 2+ provider-reported pneumonitis, with Black patients less likely to have grade 2+ provider-reported pneumonitis (odds ratio 0.37 [95% CI, 0.15 to 0.90], $P = .03$). Greater PTV size was associated with an increased likelihood of grade 2+ provider-reported pneumonitis (odds ratio 1.36 [95% CI, 1.06 to 1.75], $P = .02$).

Table 4 shows the patient- and provider-reported toxicity results at three time points, including baseline (pre-RT), end of RT, and 3 months post-RT. There were significant differences observed for the patient-reported pre-RT general pain bother score 3+ levels between White and Black race (15% versus 24%, respectively, $P = .02$), and a statistically significant difference observed for the patient-reported end of RT general pain bother score 3+ levels between White and Black race (17% versus 30%, respectively, $P = .001$). All other comparisons by race were nonsignificant. The grade 2+ pneumonitis rates were

TABLE 3. Logistic Models for Provider-Reported Toxicity

Covariate	OR	95% CI	*P*
Odds of developing grade 2+ provider-reported esophagitis			
Black *v* White race	1.27	0.91 to 1.76	.16
Esophageal D2cc centered and scaled[a] (per one SD increase)	1.96	1.70 to 2.28	**< .0001**
PTV centered and scaled[a] (per one SD increase)	0.89	0.78 to 1.00	.06
Esophagus within 2 cm of PTV	0.75	0.39 to 1.47	.40
No. of structures within 2 cm of PTV	1.18	1.00 to 1.39	.05
Stage III *v* II	1.11	0.77 to 1.58	.57
Concurrent chemotherapy	1.44	1.09 to 1.91	**.01**
Odds of developing grade 2+ provider-reported pneumonitis			
Black *v* White race	0.37	0.15 to 0.90	**.03**
PTV centered and scaled[a] (per one SD increase)	1.36	1.06 to 1.75	**.02**
Stage III *v* II	1.20	0.56 to 2.56	.64
Mean lung dose, Gy	0.98	0.86 to 1.10	.69
Lung V20, %	1.05	0.98 to 1.11	.16
Age, years	1.01	0.98 to 1.04	.43
Male sex	1.03	0.60 to 1.75	.92
Current or former smoker *v* never smoker	0.76	0.22 to 2.62	.67
COPD	1.16	0.64 to 1.87	.74

NOTE. Bold entities indicate statistically significant and marginally significant findings.
Abbreviations: COPD, chronic obstructive pulmonary disease medical comorbidity; D2cc, highest dose to 2 cc of volume; OR, odds ratio; PTV, planning target volume; SD, standard deviation; V20, volume of tissue receiving at least 20 Gy.
[a]PTV centered and scaled was defined as (PTV – mean [PTV])/SD (PTV) and a similar process was used for the centering and scaling process for the esophageal D2cc metric. See the Methods section in the manuscript for further explanation and context regarding these particular metrics.

TABLE 4. Patient- and Provider-Reported Toxicity Results

Time Point	Pretreatment		End of Treatment		3-Month Post-treatment	
Race	**White**	**Black**	**White**	**Black**	**White**	**Black**
Patient-reported bother score 3+ toxicity, % (No.)						
Side effects (general)	4.0 (30)	6.0 (7)	21 (167)	21 (26)	7 (41)	10 (8)
Cough	30 (255)	26 (40)	24 (195)	27 (34)	21 (113)	17 (15)
SOB	25 (234)	26 (37)	19 (157)	17 (21)	21 (113)	18 (15)
Chest pain	9.0 (78)	7.0 (10)	10 (79)	13 (17)	6.0 (32)	7.0 (6)
General pain	15[a] (139)	24[a] (33)	17[b] (144)	30[b] (38)	10 (56)	11 (9)
Trouble swallowing	1.0 (13)	0.4 (1)	5.0 (57)	4.0 (9)	0.3 (3)	0.9 (2)
Provider-reported grade 2+ pneumonitis, % (No.)	0.7 (8)	0 (0)	0.4 (6)	0.5 (1)	7.0 (38)	4.0 (4)
Provider-reported grade 2+ esophagitis, % (No.)	2 (17)	3 (6)	33 (338)	35 (72)	3 (16)	0 (0)

Abbreviation: SOB, shortness of breath.
[a]*P* value = .02.
[b]*P* value = .001, all other comparisons are nonsignificant.

numerically higher for White patients compared with Black patients at 3 months postradiation, although the rate of pneumonitis at baseline was nonzero for White patients. The results of the generalized linear mixed-effects model evaluating the interaction between race and time on general pain scores revealed no significant difference in the change in the percentage of patients reporting severe general pain between pre-RT and post-RT by patient race. Table 5 shows the correlation analysis results for patient- and provider-reported toxicity scales for multiple time points by race. Overall, the correlations are similar with numerically higher correlation for esophagitis in White patients at three of six time points.

Figure 1 shows the variability in patient- and provider-reported lung and esophageal toxicity. Figure 1A shows patient-reported cough bother scores relative to provider-reported pneumonitis, and Figure 1B shows patient-reported SOB bother scores relative to provider-reported pneumonitis. The Spearman rank correlations for patient-reported cough and provider-reported pneumonitis were 0.055 and 0.088 for Black and White patients, respectively. The Spearman rank correlations for patient-reported SOB and provider-reported pneumonitis were 0.063 and 0.139 for Black and White patients, respectively. Generally, neither patient-reported cough nor patient-reported dyspnea is highly correlated with pneumonitis grade, as indicated by their low Spearman rank correlation scores. Overall, for the lung PROs of cough and SOB, it was observed that White patients had greater variability in pneumonitis grades for each patient-reported bother score relative to Black patients, despite similar standard deviation ranges by race (0.16-0.53 for Black patients compared with 0.25-0.80 for White patients; Data Supplement). Another related observation is that there were proportionally more Black patients than White patients recorded as having pneumonitis grade 0 even when the patient-reported SOB and cough bother levels were scored as 3-4 (very bothersome).

Figure 1C shows the patient-reported trouble swallowing bother scores relative to provider-reported esophagitis. Esophagitis grade generally increased with patient-reported trouble swallowing for patients of both races. The Spearman rank correlations for patient-reported trouble swallowing and provider-reported esophagitis were 0.596 and 0.665 for Black and White patients, respectively. The tabulated data for Figure 1 are enumerated in the Data Supplement. The amounts of missing data for these metrics by race are shown in the Data Supplement.

DISCUSSION

In this large multi-institutional study, we found no evidence of differences in RT treatment or chemotherapy approaches by race. There were notable differences by race, however, in terms of experiencing general pain with Black patients reporting a greater amount of general pain at baseline and at the end of radiation treatment, which is concerning in the context of other studies showing that Black patients are less likely than White patients to receive adequate analgesic treatment for pain more generally[13-15] and thus, further study is needed. Additionally, we unexpectedly found that Black race was associated with lower odds of grade 2+ provider-reported pneumonitis despite similar rates by race of patient-reported symptoms of cough and SOB. It is unclear why this is the case, but it is worth noting that there were proportionally more Black patients than White patients recorded as having pneumonitis grade 0 even when the patient-reported SOB and cough bother levels were scored as 3-4 (very bothersome). Additionally, it may be because of the relatively poor concordance of provider-reported pneumonitis with any patient-reported metric, in which case further investigation is needed of better ways that patient-reported clinical and radiographic data can be integrated together and compared with the provider-reported toxicity of pneumonitis. Our formal correlation analysis did not reveal significant differences in the

TABLE 5. Concordance Analysis Between Patient- and Provider-Reported Toxicities

Time Point	Spearman Rank (95% CI) Black Race	Spearman Rank (95% CI) White Race	*P*
Cough and Pneumonitis Concordance[a]			
1-month post-RT	0.16 (−0.05 to 0.35)	0.08 (−0.01 to 0.17)	.53
3-month post-RT	0.26 (0.006 to 0.49)	0.08 (−0.02 to 0.19)	.23
6-month post-RT	0.11 (−0.16 to 0.37)	0.008 (−0.11 to 0.13)	.52
SOB and Pneumonitis Concordance[a]			
1-month post-RT	0.03 (−0.18 to 0.23)	0.10 (0.005 to 0.18)	.59
3-month post-RT	0.27 (0.01 to 0.49)	0.16 (0.06 to 0.26)	.45
6-month post-RT	−0.10 (−0.36 to 0.17)	0.13 (0.006 to 0.24)	.15
Trouble Swallowing and Esophagitis Concordance[a]			
1 week after RT start	0.37 (−0.07 to 0.70)	0.12 (−0.07 to 0.30)	.29
2 weeks after RT start	0.54 (0.38 to 0.67)	0.53 (0.47 to 0.58)	.89
3 weeks after RT start	0.55 (0.41 to 0.67)	0.67 (0.63 to 0.71)	**.06**
4 weeks after RT start	0.51 (0.35 to 0.64)	0.67 (0.62 to 0.71)	**.03**
5 weeks after RT start	0.65 (0.52 to 0.75)	0.66 (0.62 to 0.70)	.83
6 weeks after RT start	0.64 (0.23 to 0.86)	0.60 (0.48 to 0.70)	.82

NOTE. Bold entities indicate statistically significant and marginally significant findings.

Abbreviations: RT, radiation therapy; SOB, shortness of breath.

[a]Patient-reported cough, shortness of breath, and trouble swallowing are on a 5-point bother score scale between 0-4 with 0 = none; provider-reported pneumonitis and esophagitis are by Common Terminology Criteria for Adverse Events grade.

correlation of PROs and provider-graded toxicities by race. Thus, the lack of correlation between patient symptom burden and pneumonitis grade does not entirely explain the lower rates of pneumonitis in Black patients compared with White patients. It is notable that the examined patient-reported symptoms of cough and dyspnea had relatively poor correlation with provider-reported pneumonitis grade generally and therefore, better models of patient-reported symptoms of pneumonitis should be explored, perhaps with multivariable modeling that includes both clinical and radiographic findings that may better correlate with provider-reported CTCAE grades of pneumonitis.

We did not find any significant relationship between grade 2+ provider-reported esophagitis and race. Race was not a significant predictor, and neither was PTV size. Higher stage, use of concurrent chemotherapy, and a greater number of organs at risk structures within 2 cm of the PTV all predicted for increased odds of having provider-reported esophagitis, and all these variables make sense clinically.

The patient-reported general pain scores were observed to differ by race. We observed statistically higher rates of general pain in Black patients relative to White patients at baseline and at the end of treatment (at least 3+ bother score). However, there were equivalent rates of general pain by race at 3 months post-RT and no other statistically significant differences by race were observed looking at the three time points of pre-RT, end of RT, and 3 months post-RT. Moreover, the generalized linear mixed-effects model did not provide evidence that any differences observed vary by race in the percentages of patients reporting general pain between pre-RT and post-RT. The higher baseline and end of RT differences in general pain by race may be influenced by unmeasured social determinants of health, as well as access to pain medications, palliative care supportive services, and racial differences in types of medical comorbidities. Further work is needed to investigate the differences observed in general pain levels by race, which do not appear to be related to radiation treatments per se but rather to other unmeasured differences by race.

The more comprehensive correlation analysis by race of pneumonitis, esophagitis, and corresponding patient-reported toxicities revealed several insights. There were no significant differences observed in the correlation analysis by race for the three time points examined for differences between provider-reported pneumonitis and patient-reported SOB and cough. However, there was a statistically significant difference by race observed at 4 weeks after the start of RT for provider-reported esophagitis compared with patient-reported trouble swallowing. At 4 weeks after the start of RT, lower correlation was observed for Black patients than White patients (0.51 *v* 0.67, respectively, $P = .03$). There was also a marginally significant ($P = .06$) pattern observed at 3 weeks after RT start with a Spearman rank of 0.55 for Black patients compared with 0.67 for White patients. This represents a concerning pattern whereby it is possible that there are differences between patient-reported symptoms of trouble swallowing and provider-reported esophagitis grade with better correlation for White patients. Further research is needed, including a broader study of the multitude of social determinants of health affecting patient-provider communication, to determine the factors driving the racial differences observed.

In the context of other studies, there has been investigation of PROs in lung cancer more generally but the association with race has not been well studied in a large cohort. Smaller studies have provided some insight, however. Vogel et al examined patient demographics associated with worse quality of life in patients with locally advanced NSCLC receiving definitive chemoradiation. In their small study of 43 patients, among other variables such as age and female sex, it was determined that African American ethnicity was associated with worse post-treatment health-related quality-of-life measures.[16] The results of that study are not directly comparable with our study but do provide some insight that patients of minority race and ethnicity may

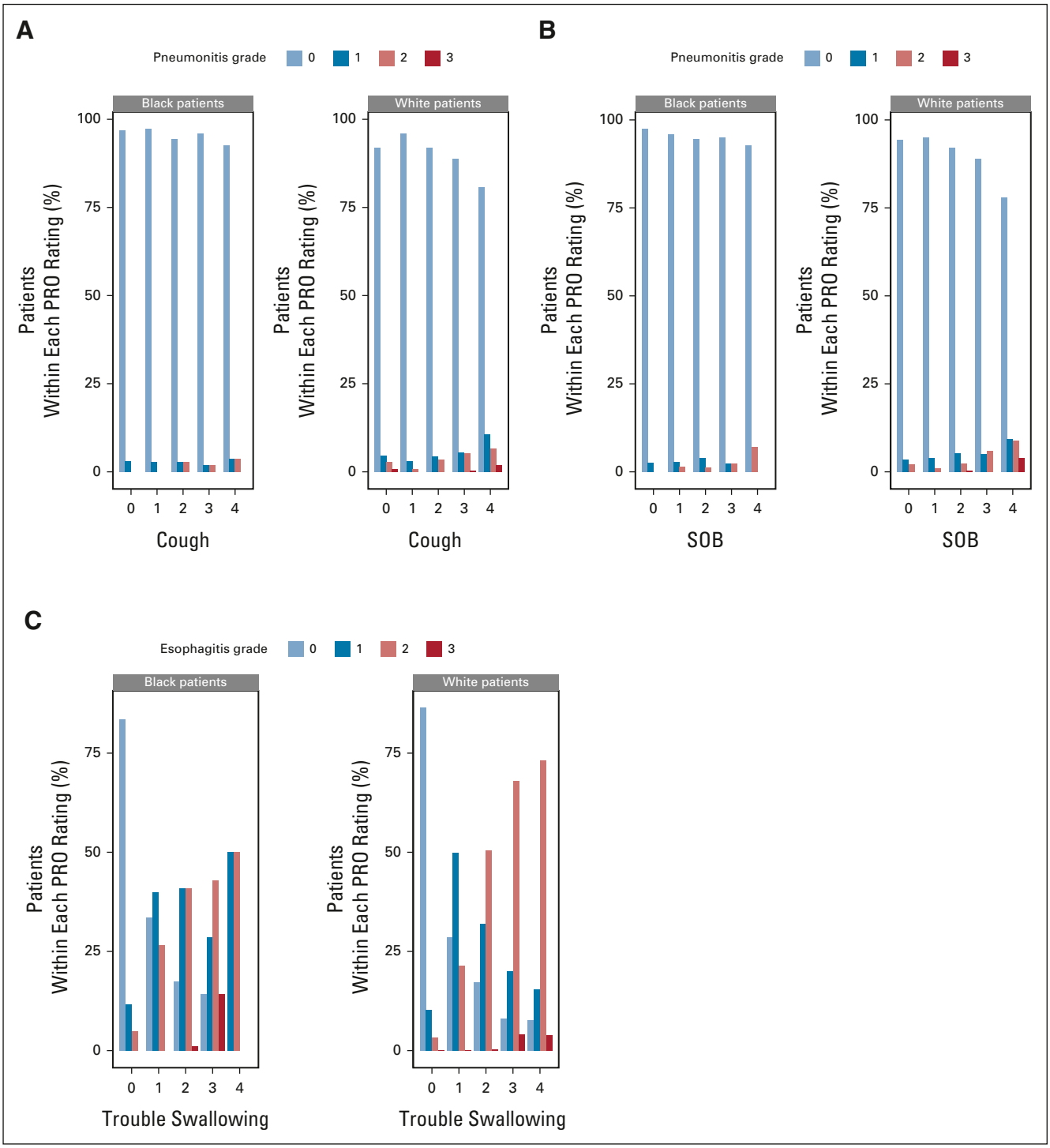

FIG 1. PROs and provider-reported toxicity. (A) A bar chart of the patient-reported cough bother score from 0 to 4 (where 0 = none) for each provider-reported pneumonitis grade for Black and White patients. (B) A bar chart of the patient-reported SOB bother score from 0 to 4 (where 0 = none) for each provider-reported pneumonitis grade for Black and White patients. A greater degree of variation in toxicity grades per PRO scores was observed for the cough and SOB bother scores for White patients compared with Black patients. (C) A bar chart of the patient-reported trouble swallowing bother score from 0 to 4 (where 0 = none) for each provider-reported esophagitis grade for Black and White patients. Esophagitis grade tended to increase with PRO scores for patients of both races. All PROs and toxicity grades are recorded as whole number scores. PRO, patient-reported outcome; SOB, shortness of breath.

experience worse quality of life and higher burden of symptoms during treatment for locally advanced NSCLC. Another study by Cykert et al of patients with early-stage lung cancer found that Black race was independently associated with a lower rate of surgical resection, which was determined to be at least partly because of the racial

differences in the perception that quality of life would be worse one year after surgery, a belief held in 42% of Blacks compared with 34% of Whites.[17,18] This study by Cykert et al provides insight into racial differences in beliefs regarding quality-of-life perceptions but is not directly comparable with our study examining actual toxicities observed. To our knowledge, no other studies have specifically assessed patient- and provider-reported differences in toxicity by race in a large cohort of prospectively studied patients with locally advanced NSCLC.

It is encouraging that there were no differences by race in treatment characteristics such as the type of RT or sequencing of chemotherapy for our database of patients with stage II-III NSCLC, particularly in light of the historical differences in surgical care that contributed to mortality differences by race for patients with lung cancer. The large statewide quality consortium represents an ideal format to broadly study cancer care treatment patterns to ensure health care equity by race and other important social determinants of health.

The differences by race in the treatment-related toxicities we observed warrant further study. Generally, there was greater variability in the toxicity grade by PRO score in White patients compared with Black patients for both lung and esophageal toxicities, with wide-ranging standard deviations in the distribution of graded toxicities. Although further research is needed to confirm our results and further investigate the driving factors, it is possible that racial differences in patient-provider communication contributed to the reported toxicity differences such that Black patients' symptoms were under-recognized in the provider-reported metrics. Recent work in patients with breast cancer has highlighted a similar narrative, that minority race patients' symptoms were under-recognized by providers in our consortium in a recently published analysis of our large statewide database.[19] Further research will be helpful to explore and develop potentially better patient-reported metrics to correlate with provider-reported pneumonitis as for both races, there was relatively poor correlation between cough, SOB, and pneumonitis compared with proportionally much better Spearman correlation values for the trouble swallowing and esophagitis comparisons. There is no available literature to suggest differences in biologic susceptibility to pneumonitis by race.

Our study has several strengths and limitations. The strengths include the large, multi-institutional, and prospectively collected nature of our database, validated patient questionnaires to collect patient-reported information, and robust statistical analyses. Some of the limitations include that causality cannot be determined because of the observational nature of the data and that not all of the contributing factors have been measured, including communication styles, provider racial demographics, or patient education level, insurance status, and other social determinants of health that may have contributed to the racial differences in toxicity observed. Although this is a large study of more than 1,000 patients and the largest study of its kind to address this particular question, there is still limited power to detect some differences because of the limited number of events. Another limitation is the amount of missing patient-reported data. Overall, 88% of patients who completed PROs at baseline also completed them at one or more of the four follow-up time points (end of treatment, 1 month, 3 months, and 6 months). Thus, we believe it is reasonable to assume the PROs are largely missing at random. Additionally, the mixed-effect models we fit provide for valid inference in the presence of some forms of informative missingness. An additional limitation is the geographic restriction of our study to a subset of centers within the state of Michigan, as racial disparities in care may vary in different regions and settings in other states within the United States as well as globally. Further research is therefore needed to evaluate the racial differences we found in the greater context of all of the factors contributing to patient-reported quality of life.

In conclusion, our findings from this large statewide consortium observational study suggest that there are no differences by race in treatment patterns of radiation design and sequencing of chemotherapy for patients with stage II-III NSCLC, which is encouraging. However, differences were observed by race for treatment-related toxicities and their recognition. Specifically, Black patients had lower rates of provider-reported pneumonitis than White patients, after controlling for several disease and treatment characteristics. There was a higher correlation between patient- and provider-reported esophageal toxicities for White patients compared with Black patients, suggesting possible under-recognition of Black patients' symptoms. Further studies are needed to understand the implications of these findings and to continue to examine the social determinants of health beyond race that contribute to the differences observed. Although these relationships are multifactorial and causality cannot be determined from our observational database, the findings may have implications for the care of racially diverse patients and warrant further research.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

We are not authorized to share MROQC data. The data are individually owned by the member institutions of MROQC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Racial Differences in Treatments and Toxicity in Patients With Non–Small-Cell Lung Cancer Treated With Thoracic Radiation Therapy

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