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Choosing Wisely? Patterns and Correlates of the Use of Hypofractionated Whole-Breast Radiation Therapy in the State of Michigan

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Summary

Based on evidence from randomized trials, consensus guidelines endorse the use of hypofractionated whole-breast radiation therapy in selected breast cancer patients receiving lumpectomy. We investigated hypofractionation use in a consortium of radiation oncology practices. The majority of patients eligible for hypofractionation continued to receive standard fractionation even in 2013, after

Purpose: Given evidence from randomized trials that have established the non-inferiority of more convenient and less costly courses of hypofractionated radiotherapy to the whole breast in selected breast cancer patients who receive lumpectomy, we sought to investigate the use of hypofractionated radiation therapy and factors associated with its use in a consortium of radiation oncology practices in Michigan. We sought to determine the extent to which variation in use occurs at the physician or practice level versus the extent to which use reflects individualization based on potentially relevant patient characteristics (such as habitus, age, chemotherapy receipt, or laterality).

Methods and Materials: We evaluated associations between receipt of hypofractionated radiation therapy and various patient, provider, and practice characteristics in a multilevel model.

Results: Of 1477 patients who received lumpectomy and whole-breast radiation therapy and were registered by the Michigan Radiation Oncology Quality Consortium (MROQC) from October 2011 to December 2013, 913 had T1-2, N0 breast cancer. Of these 913, 283 (31%) received hypofractionated radiation therapy. Among the 13 practices, hypofractionated radiation therapy use ranged from 2% to 80%. On multilevel

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publication of guidelines and mature trial results. Use varied widely between practices (2%-80%), suggesting the need for greater diffusion of evidence into practice.

analysis, 51% of the variation in the rate of hypofractionation was attributable to the practice level, 21% to the provider level, and 28% to the patient level. On multivariable analysis, hypofractionation was more likely in patients who were older (odds ratio [OR] 2.16 for age ≥50 years, $P = .007$), less likely in those with larger body habitus (OR 0.52 if separation between tangent entry and exit ≥25 cm, $P = .002$), and more likely without chemotherapy receipt (OR 3.82, $P < .001$). Hypofractionation use was not higher in the last 6 months analyzed: 79 of 252 (31%) from June 2013 to December 2013 and 204 of 661 (31%) from October 2011 to May 2013 ($P = .9$).

Conclusions: Hypofractionated regimens of whole-breast radiation therapy have been variably administered in the adjuvant setting in Michigan after the publication of long-term trial results and consensus guidelines. Most of this variability is explained at the practice and provider level rather than by patient-level features, although care is being individualized to some degree.

Introduction

Adjuvant radiation therapy is the standard of care in patients receiving breast-conserving surgery for breast cancer, given its substantial role in reducing the risk of locoregional recurrence, along with its modest impact on survival (1). The randomized trials that established the role of radiation therapy in this setting largely used standard fractionation. Therefore, historically, patients who wished to receive breast conservation were counseled that they would require at least 5 weeks of daily radiation therapy to ensure adequate disease control. This led to concerns about inadequate access to breast-conserving therapy among populations facing barriers to the receipt of protracted courses of radiation therapy (2, 3). In combination with emerging evidence suggesting that breast cancer might demonstrate a lower α/β ratio than traditionally ascribed to tumors, these concerns led to interest in exploring the efficacy and safety of hypofractionation (4).

Given cautionary historical experiences with larger fraction sizes in combination with high total doses to the whole breast, recent studies evaluated the administration of larger doses per fraction along with a reduced total dose, in an attempt to maintain normal tissue tolerance. Among the most influential of these studies was a Canadian randomized trial, which enrolled 1234 women with invasive, node-negative breast cancer and breast separation ≤25 cm, treated by lumpectomy with negative pathologic margins (5). These women were randomized to a hypofractionated course of 42.5 Gy in 16 fractions over 22 days versus a standard course of 50 Gy in 25 fractions over 35 days. An early report published in 2002 showed similar cosmetic outcomes at 3 and 5 years, with no significant difference in the excellent 5-year local recurrence-free survival in the 2 arms (97.2% vs 96.8%). British trials confirmed that toxicity and efficacy were similar with hypofractionated versus standard approaches (6-9). In 2008, the Standardisation of Radiotherapy (START) B trial, which compared 40 Gy in 15 fractions over 3 weeks with 50 Gy in 25 fractions over 5 weeks in 2215 women, found low and similar rates of locoregional recurrence (2.2% after 40 Gy and 3.3% after 50 Gy), and it actually reported lower rates of late adverse effects after hypofractionated treatment ($P = .06$ for photographic change in breast appearance) at a median follow-up of 6 years.

In 2011, after publication of long-term results from the Canadian trial demonstrated continued noninferiority of disease control without increased toxicity (10), the American Society for Radiation Oncology (ASTRO) issued an evidence-based guideline that supported the use of hypofractionation for patients aged ≥50 years with T1-2, N0 breast cancer, who did not receive chemotherapy and in whom dose homogeneity was within ±7% at central axis (11). Long-term results of British trials (12) and encouragement of hypofractionation in ASTRO's Choosing Wisely campaign (13) followed in 2013.

Although trial results have suggested that hypofractionation is not inferior for disease control and not more toxic, and a consensus panel of breast cancer experts has endorsed this approach, there has been concern about slow uptake in US clinical practice (14) as trial results accumulated. Although rates of uptake in hypofractionation in Canada have been evaluated (15), and the 2013 update of the START trials stated that the use of 40 Gy in 15 fractions had already been adopted "by most UK centres as the standard of care for women requiring adjuvant radiation therapy for invasive early breast cancer" (12), rates of uptake of this more convenient and less costly approach after the publication of long-term trial results and the ASTRO consensus guidelines remain unknown. Because a primary concern about hypofractionation relates to amplification of late toxicities, many providers may have been awaiting the long-term trial results before adopting this approach, and updated data on utilization are essential to evaluate whether evidence is appropriately influencing practice. Therefore, we investigated the use of hypofractionated radiation therapy and factors associated with its use in a consortium of radiation oncology practices in Michigan, to determine variation at the practice level and the extent to which use reflects individualization based on potentially relevant patient characteristics (such as habitus, age, chemotherapy receipt, or laterality).

Methods and Materials

We evaluated the proportion of whole-breast radiation therapy administered with hypofractionated approaches in breast cancer patients receiving lumpectomy and radiation therapy at each practice participating in the Michigan Radiation Oncology Quality Consortium (MROQC). MROQC is a Blue Cross Blue Shield of Michigan-funded initiative that includes community and academic practices that collect detailed dosimetric, clinical, and patient-reported data on all breast cancer patients receiving adjuvant whole-breast radiation therapy after lumpectomy at these practices, regardless of payor. Patients with bilateral breast cancer are excluded from this initiative.

Deidentified data are collected within the centralized MROQC database. Information includes clinical features reported by each patient's treating provider, such as patient age, body mass index (BMI), tumor histology (ductal carcinoma in situ [DCIS] vs invasive cancer), nodal status, laterality, and chemotherapy receipt. Patient-level dosimetric factors are also collected through a customized platform for physics data entry, including separation distance from tangential breast treatment field entry to exit, as well as radiation doses and doses per fraction. Other pertinent information, including distance from the patient's ZIP code of residence to the treatment facility, have also been calculated according to information provided by each treating facility. Provider identity, along with practice characteristics (academic vs community practice—defined by the teaching of resident physicians; rural vs suburban/urban location) are also present in the MROQC database and linked to each patient entry. We defined several provider factors for analysis (gender, years since medical school graduation, and US vs foreign medical school location), using the ASTRO directory and other Internet sources.

Our primary measure of interest was receipt of hypofractionated radiation therapy, which we defined as receipt of at least some radiation therapy fractions of >2 Gy to the whole breast; patients who received all radiation therapy fractions ≤2 Gy were considered to have received traditionally fractionated radiation therapy. We first described rates of hypofractionation within T1-2, N0 patients and those with DCIS. We then described the variability between providers by describing the range rates of hypofractionation for providers who had treated at least 5 MROQC patients with T1-2, N0 tumors, aged ≥50 years, without chemotherapy receipt, and with separation <25 cm. We also evaluated variability between practices, both within the overall T1-2, N0 cohort and after restriction to those not receiving chemotherapy and with separation <25 cm.

Within the T1-2, N0 patients in our database, we evaluated associations between receipt of hypofractionated radiation therapy and the potentially pertinent patient characteristics of BMI (grouped as <30 kg/m^2 vs ≥30 kg/m^2), separation (grouped as <25 cm vs ≥25 cm), laterality (left vs right breast), age (grouped as <50 vs ≥50 years), chemotherapy receipt, estrogen receptor (ER) status, hormone therapy receipt (within the ER$^+$ subgroup only), and distance from home to radiation therapy facility (grouped as >30 vs ≤30 miles). We then constructed a multilevel, multiple variable model in an attempt to explain rates of hypofractionation.

Three levels of effects were considered in the multilevel analysis: first, patient-level effects, second, provider-level effects, and third, practice-level effects. Patient-level covariates were the same as those considered in the bivariable analyses described above, except that because separation and BMI are highly correlated, only separation was used in the multiple variable modeling. Provider-level covariates were the physician's gender and years since graduating medical school; practice-level covariates were academic status and setting (urban/suburban vs rural). Beginning with the so-called "empty model," which allows for random deviations in the rate of hypofractionation by provider within practice and by practices, allowed for the calculation of the intraclass correlation coefficients and for partitioning the variance into the amounts attributable to each level of the model (16-18). To further explain the variation, all level-specific covariates were offered to the model simultaneously.

Finally, we evaluated for temporal changes in the use of hypofractionation by comparing the last 6 months of data available with the data from the initial period of data collection.

Results

Table 1 presents the characteristics of the 1477 patients registered by MROQC from October 2011 to December 2013, all of whom underwent lumpectomy and adjuvant radiation therapy to the whole breast. All patients received CT-based treatment planning, and the vast majority (96.5%) had at least some form of field segmentation. Of these patients, 913 had T1-2, N0 breast cancer; of these 913, 283 (31%) received hypofractionated radiation therapy. Specifically, among the 630 women who received standardly fractionated radiation therapy, most (68.4%) received 2-Gy fractions (and the remainder received fractions smaller than 2 Gy); 617 (97.9%) of these women also received boost treatment, and 18 (2.9%) received regional nodal treatment. Among the 283 who received hypofractionated radiation therapy, the vast majority (98.6%) received fractions of 2.5-2.7 Gy, with one patient receiving a fraction size between 2.1 and 2.5 Gy and 3 patients receiving at least one fraction >2.7 Gy; 184 (65.0%) of these women received boost treatment, and 3 (1.1%) received regional nodal treatment.

When we considered the 404 women with T1-2, N0 tumors who were aged ≥50 years, not treated with chemotherapy, and with separation <25 cm, we observed that 174 (43%) received hypofractionated radiation therapy. In addition, there were 312 DCIS patients; of these, 81 (26%) received hypofractionated radiation therapy.

Table 1 Characteristics of the sample of patients with T1-2, N0 breast cancer

Characteristic	Overall (full sample) (n=913)	Fraction size >2 Gy (n=283)	Fraction ≤2 Gy (n=630)	Subgroup aged 50+ y, with separation <25 cm, not receiving chemotherapy (n=404)
BMI (kg/m^2), mean (SD)	30.3 (7.2)	29.1 (6.1)	30.8 (7.6)	27.9 (5.2)
BMI 30+ kg/m^2	394 (43.1)	101 (35.6)	293 (46.4)	106 (26.2)
Missing	14	7	7	8
Separation (cm), mean (SD)	22.8 (3.8)	22.3 (3.3)	23.1 (4.0)	21.2 (2.5)
Separation 25+ cm	249 (27.2)	61 (21.5)	188 (29.8)	0
Laterality				
Right breast	451 (49.3)	141 (49.7)	310 (49.1)	197 (48.8)
Left breast	464 (50.7)	143 (50.4)	321 (50.9)	207 (51.2)
Age (y)				
Mean (SD)	62.1 (11.3)	65.9 (11.2)	60.3 (10.9)	66.6 (9.8)
Age 50+ y	769 (84.2)	254 (89.8)	515 (81.8)	404 (100)
Chemotherapy	262 (29.0)	38 (13.5)	224 (36.0)	0
Missing	9	2	7	0
ER positive	748 (82.3)	243 (86.8)	505 (80.3)	367 (90.8)
Missing	4	3	1	2
Hormone therapy among ER-positive cases	647 (88.3)	194 (81.9)	453 (91.3)	314 (85.6)
Missing	15	6	9	5
Histology				
Invasive ductal	790 (86.6)	241 (85.2)	549 (87.3)	343 (84.9)
Invasive lobular	75 (8.2)	23 (8.1)	52 (8.3)	41 (10.1)
Other	47 (5.2)	19 (6.7)	28 (4.4)	20 (5.0)
Missing	1	0	1	0
Surgical margins				
Negative	788 (86.9)	242 (86.7)	546 (86.9)	349 (86.4)
Close	99 (10.9)	29 (10.4)	70 (11.2)	45 (11.4)
Positive	20 (2.2)	8 (2.9)	12 (1.9)	9 (2.2)
Missing	6	4	2	1
Distance to RT facility >30 mi	78 (8.5)	30 (10.6)	48 (7.6)	32 (7.9)
Missing	3	0	3	2

Abbreviations: BMI = body mass index; ER = estrogen receptor; RT = radiation therapy.
Values are number (percentage) unless otherwise noted.

Data were analyzed from 13 facilities/hospitals, of which 6 were academic and 9 were located in an urban setting. Forty-three unique physicians treated patients, 33 of whom were male and 37 of whom graduated from a US medical school, with an average of 22 years since graduation (minimum 6, maximum 55). The average number of patients per provider was 32, and the median was 19, with each physician treating at least 1 patient and the highest-volume physician having treated 128 patients. The rate of hypofractionation use varied between 0 and 96.8% among physicians who had treated at least 5 patients with T1-2, N0 tumors, aged ≥50 years, without chemotherapy receipt, and with separation <25 cm.

As shown in Figure 1, among the 13 practices, hypofractionated radiation therapy use in T1-2, N0 breast cancer patients ranged from 2% to 80%. Similar variability existed when additional criteria were included (age ≥50 years, no chemotherapy, and separation <25 cm), with a range from 5% to 93%. On bivariable analysis, as shown in Table 2, hypofractionation was significantly more common in patients with lower BMI (odds ratio [OR] 1.52, P=.005), smaller separation (OR 1.55, P=.009), older age (OR 1.96, P=.003), and nonreceipt of chemotherapy (OR 3.59, P<.001), positive ER status (OR 1.61, P=.019), and hormone receipt within the ER$^+$ subgroup (OR 2.34, P<.001). Figure 2 depicts rates of hypofractionation use by patient subgroups stratified by age, separation length, and chemotherapy use.

On multilevel analysis, the 3-level "empty model" suggested that 50.7% of the variation in the rate of hypofractionation could be attributed at the hospital level, with 20.9% attributed to the provider level, and 28.4% attributed to the patient level. As shown in Table 3, on the multilevel, multiple variable analysis, hypofractionation was more likely in patients who were older (OR 2.16 for age ≥50 years, P=.007), less likely with larger body habitus (OR 0.52 if separation between tangent entry and exit ≥25 cm, P=.002), and more likely without chemotherapy receipt (OR 3.82 among those not receiving chemotherapy, P<.001). The multilevel, multiple variable model suggested that none of the provider-level (gender P=.6, years since graduation P=.9) or practice-level covariates (academic

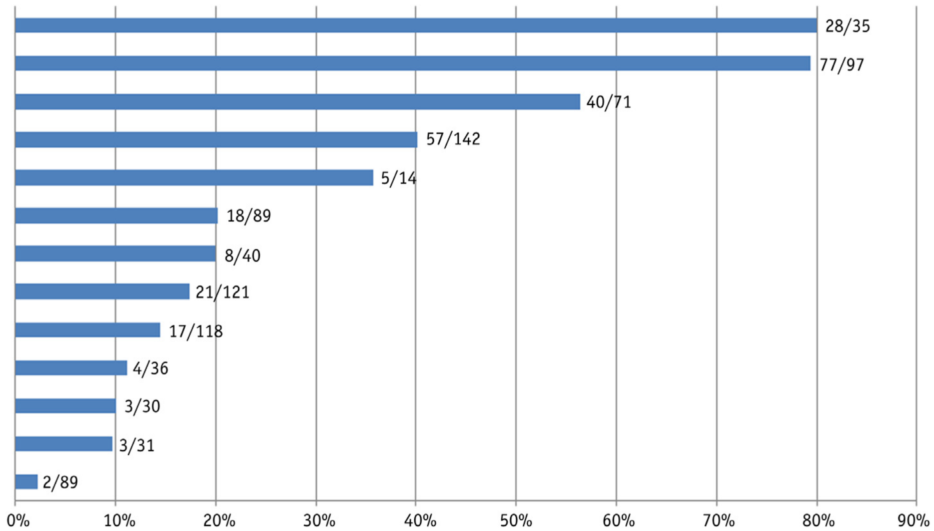

Fig. 1. Rates of hypofractionation use by institution for patients with T1-2, N0 tumors treated with lumpectomy and whole-breast radiation therapy (n=913).

status $P=.3$ and urban/suburban vs rural $P=.2$) or other variables evaluated was significantly associated with hypofractionation receipt.

Finally, hypofractionation use was not higher in the last 6 months analyzed. Hypofractionation was used in 79 of 252 (31%) of the T1-2, N0 patients registered from June 2013 to December 2013 and 204 of 661 (31%) registered from October 2011 to May 2013 ($P=.9$).

Discussion

In this study of practice patterns in a consortium of radiation oncology practices in the state of Michigan, we found dramatic variations in the use of hypofractionated approaches from center to center, even after the publication of long-term results from randomized trials and consensus guidelines. Moreover, the majority of patients treated by practices in this consortium continued to receive long courses of standard fractionation even in the most recent months of data collection and even after restricting to those who were older, did not receive chemotherapy, and lacked large body habitus. These findings raise concerns about the diffusion of evidence into practice in this context; they also serve to demonstrate the value of radiation oncology–specific registries in providing timely data on practice patterns, including the ability to consider potentially pertinent patient-level characteristics, such as breast separation, that are not available in other data sets.

Previous studies have shown that uptake of hypofractionation has been variable even in the Canadian province of Ontario, from which seminal evidence regarding this approach emerged, but less has been known about practice patterns within the United States (19), and even less about the extent to which variability reflected

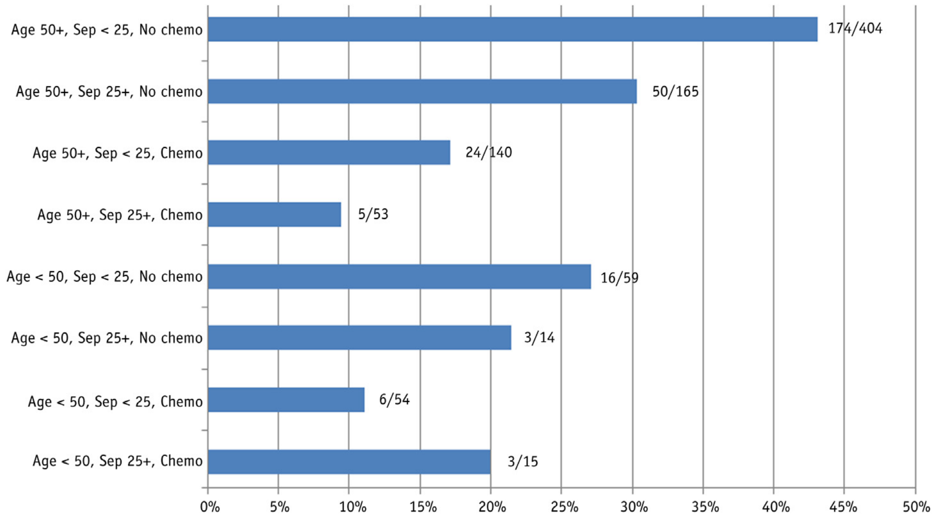

Fig. 2. Rates of hypofractionation use by patient subgroups stratified by age, separation length, and chemotherapy use (n=913).

Table 2 Bivariable and multivariable patient-level associations (ignoring higher-level variation) with hypofractionation (n=913)

Characteristic	Bivariable associations OR	95% CI	*P*	Multivariable associations* OR	95% CI	*P*
BMI <30 vs 30+ kg/m^2	1.52	1.13-2.04	.005			
Separation <25 vs 25+ cm	1.55	1.11-2.16	.009	1.64	1.16-2.33	.005
Laterality: right vs left	1.03	0.78-1.36	.83	0.96	0.71-1.29	.763
Age 50+ vs < 50 y	1.96	1.27-3.02	.003	1.74	1.09-2.78	.021
Chemotherapy: no vs yes	3.59	2.46-5.24	<.001	3.82	2.47-5.91	<.001
ER status: positive vs negative	1.61	1.08-2.40	.019	0.84	0.53-1.35	.478
Hormone therapy†: none vs yes	2.34	1.48-3.68	<.001			
Histology: lobular vs ductal	1.01	0.60-1.68	.997	0.86	0.51-1.47	.589
Other vs ductal	1.55	0.85-2.82	.156	1.28	0.68-2.42	.439
Surgical margins: positive vs negative	1.50	0.61-3.73	.378	1.71	0.64-4.54	.281
Close vs negative	0.94	0.59-1.48	.773	0.94	0.59-1.52	.811
Distance to RT facility >30 vs ≤ 30 mi	1.43	0.88-2.31	.15	1.57	0.93-2.64	.09

Abbreviations: CI = confidence interval; OR = odds ratio. Other abbreviations as in Table 1.

* Hormone therapy and BMI were not included in the multivariable model owing to strong association with other model variables ER status and separation length, respectively.

† Hormone therapy association calculated only for the bivariable association and those cases known to be ER positive (n=748).

patient-level individualization versus provider- and practice-level factors. Preliminary analysis of elderly patients in the Surveillance, Epidemiology, and End Results—Medicare database has suggested that rates of hypofractionation remained low even in the oldest elderly patients in that sample in 2010, the most recent year for which data are available from that population-based national database (14). This has raised concerns about the extent to which evidence has diffused into practice and the possibility that financial incentives might be inappropriately dampening enthusiasm for this approach.

However, many providers may have had reasonable concerns about uptake of hypofractionation, including appropriately individualized considerations of whether these results should be applied to patients with larger body habitus than those on clinical trials, as well as whether they could be extrapolated to patients with DCIS or those receiving chemotherapy. Providers may have had particularly high thresholds for patients with left-sided disease, due to concerns about late cardiac toxicity with larger fraction sizes, and they may have been awaiting long-term results that were not available until the end of the period from which data are available in the most recent releases of large national data sets. Therefore, it was particularly important to evaluate use in a more updated data set with access to potentially pertinent patient-level factors that could be evaluated within a multilevel analytical approach that also considered the influence of provider- and practice-level factors.

Table 3 Multilevel, multiple variable model for hypofractionation (n=913)

Fixed effects	OR	95% CI	*P*
Separation 25+ vs < 25 cm	0.52	0.34-0.79	.002
Age 50+ vs < 50 cm	2.16	1.24-3.76	.007
Chemotherapy: no vs yes	3.82	2.41-6.06	<.001

Abbreviations as in Table 2.

In the present study, use of hypofractionation did vary by patient characteristics, suggesting that providers may be appropriately considering the possibility of greater toxicity from hypofractionated approaches in patients with larger body habitus and the paucity of data regarding the appropriateness of hypofractionation in patients who receive chemotherapy (who were not well represented in the randomized trials investigating hypofractionation). Lower use in younger patients also suggests some appropriate individualization of care, given that younger patients were not well represented on trials, leading to concerns about the possibility of undertreating a population known to receive higher absolute benefits from radiation therapy than older patients (concerns that led consensus guidelines only to recommend hypofractionation in patients aged ≥50 years). Rates of hypofractionation were not much lower in patients with DCIS than they were in patients with T1-2, N0 disease, suggesting that providers who have embraced this approach may feel reasonably comfortable extrapolating beyond patients with invasive disease.

Nevertheless, most of the variability in utilization observed in this study was at the practice and provider level. Although we were unable to identify specific practice or provider characteristics that were associated with hypofractionation use, the multilevel model results suggest that differences in use are likely to reflect differences in factors such as physician attitudes, knowledge, and incentives. These findings motivate ongoing efforts within MROQC and elsewhere to improve provider recognition that this approach may be underused and investigation into interventions that may increase its uptake, informed by the rich literature on physician practice change (20).

This study had a number of strengths, including access to a database designed by radiation oncologists for the collection of data relevant for radiotherapeutic decision making. Radiation oncology—specific registries (21) have substantial promise for the investigation of research questions such as those posed here. As in this case, they may facilitate the particularly nimble evaluation of very recent patterns of care in ways that large national databases may fail to allow. The combination of data on patient-, provider-, and practice-level factors provides a relatively unique opportunity for sophisticated application of analytical methods such as the multilevel analysis conducted here. However, the present study also has limitations. The observation of associations between utilization and certain covariates can only begin to illuminate the reasons that hypofractionation is so infrequently used in some settings and so frequently used in others. Further research is necessary using techniques other than observational analysis of utilization, including patient and provider surveys, to more deeply elucidate these important issues. Other limitations of the present work include the relatively smaller size of the sample compared with that available in other databases and the fact that it includes practices and patients within a single state who are participating in the quality consortium MROQC. Nevertheless, to the extent that we observe dramatic variability, we find it particularly striking that this extent of variability was observed in a single state. We believe it is also important to emphasize that although MROQC is funded by a specific insurer, data were collected on all patients within participating practices, regardless of insurance type. Because we are unaware of any larger sources of up-to-date data on practice patterns within the United States, we believe the present analysis is both timely and highly relevant.

In recent years there has been growing recognition that physicians have a duty to deliver patient-centered care and to serve as responsible stewards of scarce resources for health care (22). To fulfill this duty, it is critical to ensure translation of research findings regarding less burdensome approaches to radiation therapy into practice. Studies like the present one are important if we are to understand how best to ensure appropriately individualized care to our patients in light of evolving evidence, as well as to illuminate how to reap maximal impact from ongoing studies also seeking creatively to lessen the burden of radiation therapy (23, 24).

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