CLINICAL INVESTIGATION

Comparative Effectiveness Analysis of 3D-Conformal Radiation Therapy Versus Intensity Modulated Radiation Therapy (IMRT) in a Prospective Multicenter Cohort of Patients With Breast Cancer

Reshma Jagsi, MD, DPhil,* Kent A. Griffith, MS, MPH,† Jean M. Moran, PhD,* Martha M. Matuszak, PhD,* Robin Marsh, CMD,* Margaret Grubb, MS,* Eyad Abu-Isa, MD,*†† Joshua T. Dilworth, MD, PhD,* Michael M. Dominello, DO,* David Heimburger, MD,‡ Danielle Lack, MS,* Eleanor M. Walker, MD,* James A. Hayman, MD,* Frank Vicini, MD,* and Lori J. Pierce, MD* on behalf of the Michigan Radiation Oncology Quality Consortium

*Department of Radiation Oncology, Medical School, University of Michigan, Ann Arbor, Michigan; †Department of Biostatistics, University of Michigan, Ann Arbor, Michigan; ‡Department of Radiation Oncology, Providence Ascension, Novi, Michigan; §Department of Radiation Oncology, Beaumont Health, Royal Oak, Michigan; ††Department of Radiation Oncology, Karmanos Cancer Center, Wayne State University, Detroit, Michigan; †‡Department of Radiation Oncology, Munson Healthcare, Traverse City, Michigan; †††Department of Radiation Oncology, Henry Ford Health System, Detroit, Michigan; and †‡‡Department of Radiation Oncology, GenesisCare, Farmington Hills, Michigan

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Purpose: Simple intensity modulation of radiation therapy reduces acute toxicity compared with 2-dimensional techniques in adjuvant breast cancer treatment, but it remains unknown whether more complex or inverse-planned intensity modulated radiation therapy (IMRT) offers an advantage over forward-planned, 3-dimensional conformal radiation therapy (3DCRT).

Corresponding author: Reshma Jagsi, MD, DPhil; E-mail: rjagsi@med.umich.edu

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Data are owned by the local collaborating sites and therefore the Michigan Radiation Oncology Quality Consortium is not permitted to share the data used for this study.

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Methods and Materials: Using prospective data regarding patients receiving adjuvant whole breast radiation therapy without nodal irradiation at 23 institutions from 2011 to 2018, we compared the incidence of acute toxicity (moderate-severe pain or moist desquamation) in patients receiving 3DCRT versus IMRT (either inverse planned or, if forward-planned, using ≥5 segments per gantry angle). We evaluated associations between technique and toxicity using multivariable models with inverse-probability-of-treatment weighting, adjusting for treatment facility as a random effect.

Results: Of 1185 patients treated with 3DCRT and conventional fractionation, 650 (54.9%) experienced acute toxicity; of 774 treated with highly segmented forward-planned IMRT, 458 (59.2%) did; and of 580 treated with inverse-planned IMRT, 245 (42.2%) did. Of 1296 patients treated with hypofractionation and 3DCRT, 432 (33.3%) experienced acute toxicity; of 709 treated with highly segmented forward-planned IMRT, 227 (32.0%) did; and of 623 treated with inverse-planned IMRT, 164 (26.3%) did. On multivariable analysis with inverse-probability-of-treatment weighting, the odds ratio for acute toxicity after inverse-planned IMRT versus 3DCRT was 0.64 (95% confidence interval, 0.45-0.91) with conventional fractionation and 0.41 (95% confidence interval, 0.26-0.65) with hypofractionation.

Conclusions: This large, prospective, multicenter comparative effectiveness study found a significant benefit from inverse-planned IMRT compared with 3DCRT in reducing acute toxicity of breast radiation therapy. Future research should identify the dosimetric differences that mediate this association and evaluate cost-effectiveness. © 2021 Elsevier Inc. All rights reserved.

Intensity modulated radiation therapy (IMRT) in breast cancer typically refers to the division of the radiation treatment beam delivered from any single angle into smaller subsegments that differ in intensity. This intensity modulation can be simple, involving only a few crude segments that can be planned by a human dosimetrst, or more complex (Fig. E1). At the extreme, it can involve pixel-by-pixel variation of small regions, such as each square centimeter of a treatment field, requiring inverse treatment planning. Inverse planning can also be used to deliver simpler forms of segmentation.

Randomized trials evaluating simple IMRT in the adjuvant treatment of breast cancer after lumpectomy revealed significant reductions in toxicity with this approach, compared with 2-dimensional treatment planning. However, the IMRT approach evaluated in those studies was frequently forward-planned and similar to what many US centers would call 3-dimensional conformal radiation therapy (3DCRT) rather than IMRT, which, in the United States, has most frequently been defined by insurers as treatment involving the division of at least 1 beam into 5 or more segments and often involves inverse planning.

Because IMRT delivery fees have historically been considerably higher—at one point more than double the rate of 3DCRT in the Center for Medicare Services fee schedules—stakeholders have wondered whether more complex IMRT is necessary to reduce toxicity or whether the use of 3DCRT might suffice. Unfortunately, given the rapid adoption of IMRT technology, a randomized trial directly comparing 3DCRT to more sophisticated forms of IMRT has not been feasible in the United States, although a Korean trial recently reported findings of reduced toxicity with IMRT among patients receiving conventionally fractionated breast radiation therapy. Over the past decade, practice patterns have diverged considerably among institutions, and comparison of these 2 approaches in real-world practice in the United States remains a key topic that must be examined to ensure appropriate direction of clinical practice.

Therefore, in 2011, with funding from Blue Cross Blue Shield of Michigan, we initiated a multicenter collaborative quality initiative, the Michigan Radiation Oncology Quality Consortium (MROQC), with a primary objective of evaluating the effect of IMRT in patients with breast cancer and lung cancer. This article reports the primary outcomes analysis of the large, prospective observational study that was designed to allow for meaningful comparative effectiveness analysis of 3DCRT versus more complex forms of IMRT for the treatment of breast cancer. Findings of the primary outcomes analysis in lung cancer will be presented separately. Our primary aims were to compare acute toxicity with each technique after controlling for relevant patient factors.

Data collection and sample

We obtained institutional review board approval to collect prospectively a rich array of treatment planning data and physician assessments for all eligible patients treated at MROQC member institutions with whole breast radiation therapy, as part of a quality improvement initiative. Eligible patients were women being treated with adjuvant whole breast radiation therapy for nonmetastatic, unilateral breast cancer without having breast implants at an MROQC-participating institution. We also obtained institutional review board approval to collect patient-reported data from patients who consented to participate in weekly surveys while on treatment.

Our sample was derived from the 8228 patients with breast cancer who met the analytical eligibility criteria and received adjuvant whole breast radiation therapy at 24 institutions participating in the MROQC between November 2011 and September 2018. Analytical eligibility criteria included having data sufficient to identify fraction size, treatment technique (number of segments per beam and inverse versus forward planning), and submission of a
composite treatment dose-volume histogram for the breast. We required that all patients included in the analytical sample have an end-of-treatment toxicity assessment (±7 days from date of last fraction). We further limited this sample to similarly treated cases, defined as receiving a boost, without nodal treatment, and treated in the supine position for breast and boost treatment. Finally, we required at least 10 analytically eligible cases from each treating institution, resulting in the exclusion of 9 patients from 1 institution from the analytical sample, with the smallest remaining institutional contribution 22 cases and the largest contribution 471.

We considered 5167 cases in total: 2539 patients treated with conventional fractionation and 2628 treated with hypofractionation (defined as utilizing a dose per fraction greater than 2.0 Gy). Figure 1 details the flow of patients into the analytical sample.

**Measures**

The primary, predefined outcome measure was clinically meaningful acute toxicity, defined using the maximum value recorded on any on-treatment weekly evaluation or the end-of-treatment evaluation. Clinically meaningful acute toxicity was defined ex ante to include either moderate to severe pain or moist desquamation. Pain was primarily patient reported, using an approved modification of the Brief Pain Inventory, in 3947 cases (76.4%) and physician-reported using the Common Terminology Criteria for Adverse Events (CTCAE) scale in the 1220 (23.6%) cases where patient self-report was not provided. Moist desquamation was physician reported, using a single item assessing presence or absence of any moist desquamation.

The primary independent variable of interest was treatment technique. Treatment technique was defined as 3DCRT versus 2 forms of IMRT. All patients treated with inverse planning were grouped together and categorized as having received inverse-planned IMRT. Those treated with forward planning were categorized as having received highly segmented forward-planned IMRT if there was use of ≥5 or more segments per any unique gantry angle for the primary breast plan; the remainder were categorized as receiving 3DCRT (see Fig. 2 for the distributions of treatment techniques by treating facility).

Covariates used for the creation of propensity scores for adjustment in the multivariable models were age, race (White, Black, or other), hypertension, diabetes, body mass index (BMI), chemotherapy receipt, whether the institution was an academic center (trains residents or fellows), separation distance (the distance separating the entry points of typical tangential beams at the midline and midaxillary line, which reflects an aspect of the patient’s body habitus that influences the dose homogeneity of radiation treatment), breast volume, and D50 to the treated region (the maximum dose delivered to 50% of the target volume, which serves as a proxy for differences in dose prescription).

**Statistical analysis**

We first described the study sample separately for patients treated with conventional fractionation and those treated with hypofractionation, given prior work suggesting that these 2 groups had substantially different rates of acute toxicity. We described the incidence of acute toxicity and evaluated the observed, unadjusted association between technique and toxicity in this unweighted sample.

Next, we developed propensity scores to allow for analyses using the inverse probability of treatment weighting (IPTW), whereby each patient is weighted by the inverse of the probability of the treatment actually received (effectively
up-weighting cases that had a low probability of receiving the treatment that was actually received). The propensity scores were calculated from a standard multinomial regression model predicting which treatment technique was received, using all of the covariates listed earlier. The goal of this propensity score creation and use of IPTW was to create weighted samples by treatment received that have balanced external covariates, a statistical method to make observational data resemble a randomized controlled trial. By balancing these important covariates through weighting, an unbiased and unconfounded comparison by treatment received could then be made.

Next, we estimated models using the IPTW sample. Specifically, we developed generalized linear models for the binary outcome of acute toxicity using the logit link for the binomial distribution to determine the association with treatment technique, estimated as odds ratios, in each fractionation subgroup separately, after adjustment for all covariates and including the institution of treatment as a random effect (which adjusts for differences in outcome related to clustering of patients within each treating facility). Finally, we conducted a sensitivity analysis that further subdivided the inverse-planned cases into 2 subgroups (those with ≥5 segments per any unique gantry angle and those with <5 segments for all unique gantry angles).

In addition to analyses focused on the ex ante predefined primary endpoint, we also evaluated the frequency of 2 additional endpoints: grade 3 toxicity as measured by the CTCAE and toxicity-related treatment breaks, using IPTW for weighting of percentages and P values for comparisons among the 3 treatment groups.

**Results**

Tables 1 and 2 show the characteristics of the analyzed sample by fractionation. Mean age was 58.5 years for the conventionally fractionated sample and 62.5 years for the hypofractionated sample. Numerous measured covariates differed among patients treated with 3DCRT, those treated with highly segmented forward-planning, and those treated with inverse IMRT within each fractionation subset. As expected, these imbalances were much less after application of IPTW (Table E1).

Of the 1185 patients treated with 3DCRT and conventional fractionation, 650 (54.9%) experienced acute toxicity; of 774 treated with highly segmented forward-planned IMRT, 458 (59.2%) did; and of 580 treated with inverse-planned IMRT, 245 (42.2%) did. Of 1296 patients treated with hypofractionation and 3DCRT, 432 (33.3%) experienced acute toxicity; of 709 treated with highly segmented forward-planned IMRT, 227 (32.0%) did; and of 623 treated with inverse-planned IMRT, 164 (26.3%) did. As noted in the Methods and Materials section, the acute toxicity endpoint included patient reports of pain where available (81.9% of conventionally fractionated cases treated with...
3DCRT, 76.0% treated of conventionally fractionated cases treated with highly segmented forward-planned IMRT, and 76.0% of conventionally fractionated cases treated with inverse planned IMRT cases; 78.9% of hypofractionated cases treated with 3DCRT, 66.6% of hypofractionated cases treated highly segmented forward-planned IMRT, and 73.4% of hypofractionated cases treated with inverse planned IMRT). For the other patients, acute toxicity was entirely based on physician reports.

Table 3 shows the results of models, including a crude unadjusted comparison and 3 multivariable models using the IPTW sample: one with weighting alone, one adding covariates, and a final adding hospital site as a random effect. As shown, in certain models in the hypofractionated sample, there was a significant benefit from highly segmented IMRT, but the clearest difference was between inverse-planned IMRT and 3DCRT, which was observed in all models.

The forest plots in Figures 3 and 4 detail the final models. In those models, the odds ratio for acute toxicity after inverse-planned IMRT compared with 3DCRT was 0.64 (95% confidence interval, 0.45-0.91) in patients receiving conventional fractionation and 0.41 (95% confidence interval, 0.26-0.65) in patients receiving hypofractionation. On sensitivity analysis that subdivided the inverse-planned cases into 2 subgroups based on number of segments,
findings were consistent in both magnitude and direction when each of these subgroups was compared with 3DCRT, both in patients receiving conventional fractionation and those receiving hypofractionation, suggesting that our primary approach of pooling the inverse-planned cases in a single category for analysis was appropriate.

Extremely severe toxicity was rare in all groups. For hypofractionated cases, CTCAE grade 3 radiation dermatitis occurred in 2.4% of patients treated with 3DCRT, 1.8% of those treated with highly segmented forward-planned IMRT, and 1.6% of those treated with inverse-planned IMRT ($P = .043$). Similarly, treatment breaks due to toxicity were rare in either fractionation group. For hypofractionated cases, toxicity-related treatment breaks occurred in 0.3% receiving 3DCRT, 0% of those receiving highly segmented forward-planned IMRT, and 0.8% of those receiving inverse-planned IMRT ($P = .053$). In conventionally fractionated cases, toxicity-related treatment breaks occurred in 5.0% of patients treated with 3DCRT, 2.1% of those treated with highly segmented forward-

### Table 2  Sample characteristics, hypofractionated (N = 2628)

<table>
<thead>
<tr>
<th>Variable/level</th>
<th>Statistics</th>
<th>Total population</th>
<th>3DCRT (N = 1296)</th>
<th>Highly segmented forward-planned (N = 709)</th>
<th>Inverse-planned IMRT (N = 623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) mean (SD)</td>
<td>62.53 (10.03)</td>
<td>62.27 (9.82)</td>
<td>63.7 (10.04)</td>
<td>61.72 (10.34)</td>
<td></td>
</tr>
<tr>
<td>Race N (%)</td>
<td>2094 (79.68)</td>
<td>1157 (89.27)</td>
<td>443 (62.48)</td>
<td>494 (79.29)</td>
<td></td>
</tr>
<tr>
<td>Black N (%)</td>
<td>395 (15.03)</td>
<td>84 (6.48)</td>
<td>232 (32.72)</td>
<td>79 (12.68)</td>
<td></td>
</tr>
<tr>
<td>Other N (%)</td>
<td>139 (5.29)</td>
<td>55 (4.24)</td>
<td>34 (4.80)</td>
<td>50 (8.03)</td>
<td></td>
</tr>
<tr>
<td>Hypertension No N (%)</td>
<td>1729 (65.79)</td>
<td>904 (69.75)</td>
<td>424 (59.80)</td>
<td>401 (64.37)</td>
<td></td>
</tr>
<tr>
<td>Yes N (%)</td>
<td>899 (34.21)</td>
<td>392 (30.25)</td>
<td>285 (40.20)</td>
<td>222 (35.63)</td>
<td></td>
</tr>
<tr>
<td>Diabetes No N (%)</td>
<td>2342 (89.12)</td>
<td>1180 (91.05)</td>
<td>600 (84.63)</td>
<td>562 (90.21)</td>
<td></td>
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<tr>
<td>Yes N (%)</td>
<td>286 (10.88)</td>
<td>116 (8.95)</td>
<td>109 (15.37)</td>
<td>61 (9.79)</td>
<td></td>
</tr>
<tr>
<td>Smoking status never N (%)</td>
<td>1502 (57.15)</td>
<td>770 (59.41)</td>
<td>391 (55.15)</td>
<td>341 (54.74)</td>
<td></td>
</tr>
<tr>
<td>Former N (%)</td>
<td>829 (31.54)</td>
<td>396 (30.56)</td>
<td>225 (31.73)</td>
<td>208 (33.39)</td>
<td></td>
</tr>
<tr>
<td>Current N (%)</td>
<td>297 (11.30)</td>
<td>130 (10.03)</td>
<td>93 (13.12)</td>
<td>74 (11.88)</td>
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</tr>
<tr>
<td>Hormone therapy missing N (%)</td>
<td>27 (1.03)</td>
<td>14 (1.08)</td>
<td>4 (0.56)</td>
<td>9 (1.44)</td>
<td></td>
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<tr>
<td>No N (%)</td>
<td>2206 (83.94)</td>
<td>1065 (82.18)</td>
<td>606 (85.47)</td>
<td>535 (85.87)</td>
<td></td>
</tr>
<tr>
<td>Yes N (%)</td>
<td>415 (15.79)</td>
<td>226 (17.44)</td>
<td>101 (14.25)</td>
<td>88 (14.13)</td>
<td></td>
</tr>
<tr>
<td>Group stage 0 N (%)</td>
<td>596 (22.68)</td>
<td>260 (20.06)</td>
<td>168 (23.70)</td>
<td>168 (26.97)</td>
<td></td>
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<tr>
<td>1 N (%)</td>
<td>1567 (59.63)</td>
<td>821 (63.35)</td>
<td>425 (59.94)</td>
<td>321 (51.52)</td>
<td></td>
</tr>
<tr>
<td>2 N (%)</td>
<td>462 (17.58)</td>
<td>213 (16.44)</td>
<td>115 (16.22)</td>
<td>134 (21.51)</td>
<td></td>
</tr>
<tr>
<td>3 N (%)</td>
<td>3 (0.11)</td>
<td>2 (0.15)</td>
<td>1 (0.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Separation distance (cm) Mean (SD)</td>
<td>22.54 (3.50)</td>
<td>21.98 (3.22)</td>
<td>23.26 (3.49)</td>
<td>22.87 (3.88)</td>
<td></td>
</tr>
<tr>
<td>BMI category underweight/normal &lt;25 N (%)</td>
<td>728 (27.70)</td>
<td>398 (30.71)</td>
<td>140 (19.75)</td>
<td>190 (30.50)</td>
<td></td>
</tr>
<tr>
<td>Overweight 25-&lt;30 N (%)</td>
<td>863 (32.84)</td>
<td>457 (35.26)</td>
<td>214 (30.18)</td>
<td>192 (30.82)</td>
<td></td>
</tr>
<tr>
<td>Obesity III 30-&gt;40 N (%)</td>
<td>275 (10.46)</td>
<td>106 (8.18)</td>
<td>111 (15.66)</td>
<td>58 (9.31)</td>
<td></td>
</tr>
<tr>
<td>Breast total volume (cm³) Mean (SD)</td>
<td>1038.83 (561.61)</td>
<td>944.86 (479.10)</td>
<td>1147.88 (592.33)</td>
<td>1110.2 (646.37)</td>
<td></td>
</tr>
<tr>
<td>D50 Breast (Gy) Mean (SD)</td>
<td>45.18 (2.39)</td>
<td>44.76 (2.23)</td>
<td>45.55 (2.59)</td>
<td>45.65 (2.33)</td>
<td></td>
</tr>
<tr>
<td>Treatment facility academic No N (%)</td>
<td>1553 (59.09)</td>
<td>1075 (82.95)</td>
<td>398 (56.14)</td>
<td>80 (12.84)</td>
<td></td>
</tr>
<tr>
<td>Yes N (%)</td>
<td>1075 (40.91)</td>
<td>221 (17.05)</td>
<td>311 (43.86)</td>
<td>543 (87.16)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** 3DCRT = 3-dimensional conformal radiation therapy; BMI = body mass index; IMRT = intensity modulated radiation therapy; IPTW = inverse probability of treatment weighting.
planned IMRT, and 3.6% of those treated with IMRT (P = .003). Note that the percentages and P values presented here were weighted by IPTW.

**Discussion**

In this large, prospective, multicenter comparative effectiveness analysis, we observed a statistically significant overall benefit from the use of inverse-planned IMRT compared with 3DCRT in adjuvant whole breast radiation therapy. The observed benefit was modest in magnitude, but it reflected a difference in a measure of acute toxicity (moderate or severe pain or moist desquamation) that was intentionally defined a priori to be clinically meaningful. As in prior studies, toxicity was less common in patients who received hypofractionation, but even in this group, there was a significant additional reduction of acute toxicity from the use of inverse-planned IMRT. Our findings suggest that the use of inverse planning may help to minimize the acute toxicity of treatment. These findings must be considered in the context of the evolving costs associated with more complex treatment planning and delivery, with important implications for clinical practice and policy.

The current study findings complement and extend the results of other studies investigating the optimal approach for whole breast radiation therapy. As noted earlier, prior randomized trials compared simpler forms of forward-planned intensity modulation to 2-dimensional treatment planning and demonstrated clinically significant benefits, as also demonstrated in observational studies. In a Canadian trial in 358 patients, fewer who were treated with simple IMRT experienced moist desquamation (31.2% with IMRT vs 47.8%, P = .002). In a large British trial of 1145 patients, those randomized to forward-planned simple IMRT were less likely to have suboptimal overall cosmesis (odds ratio on multivariable modeling, 0.65; P = .038) or skin telangiectasia (odds ratio, 0.57; P = .031) at 5 years. The majority of studies have focused on using IMRT (forward or inversely planned) to decrease the percent of breast tissue receiving >107% dose while increasing the proportion of the target volume receiving 95% of the prescription dose.

Several observational studies with smaller sample sizes have compared IMRT delivery (with either forward or inverse-planning) to 3DCRT. One such study considered patients treated in the prone position with moderate hypofractionation, comparing dosimetric parameters and outcomes in 57 patients who received IMRT delivery (which was used when insurers agreed to reimburse for it) to those in 40 patients who received 3DCRT (because their insurers refused coverage for IMRT). In that study, the delivery was a combination of 3-dimensional tangents (67% of the dose) and inverse-planned intensity modulated fields (33%), which not only affected dosimetric parameters such as maximum dose and dose homogeneity but was also associated with a reduced frequency of grade 2 dermatitis (13% vs 2%).

Recently, results emerged from KROG 15-03, a randomized trial of conventionally fractionated IMRT in 1.8 Gy fractions to the whole breast with simultaneous integrated boost versus conventionally fractionated 3DCRT with sequential boost. Consistent with the observations in the current study, the trial showed lower skin toxicity with IMRT and no difference in locoregional recurrence. Specifically, the incidence of grade ≥2 dermatitis as assessed by clinicians was significantly lower in the IMRT arm (37.1% vs 47.8%, P = .002).
Our study complements this trial by offering evidence from a variety of practice settings in the United States, incorporating patient-reported outcomes and including patients treated with hypofractionation. The consistent findings of our carefully controlled observational comparative effectiveness study, optimized for generalizability to real-world practice in the United States, and this recent randomized trial, optimized for causal inference, are compelling.

When IMRT was first developed, substantial additional costs and resources were required for its delivery. Over time, these differences have decreased, thanks to efforts to develop and disseminate both simple IMRT techniques and more complex but efficient approaches. Differences in fee schedules for reimbursement of radiation therapy using different techniques have led both to concerns about the possible overuse of IMRT in the United States, driven by higher reimbursement, and also concerns about how the lack of nuance in billing codes might potentially stifle innovation and drive underuse of IMRT, due to a desire to responsibly steward resources. Although current Medicare fee schedules no longer reimburse IMRT at dramatically higher rates than 3DCRT and bundled payments will soon be explored at some sites, payments by some private insurers diverge considerably even today. Ultimately, determining whether widespread use of more complex forms of IMRT for whole breast irradiation should be recommended will require weighing the likelihood and magnitude of
expected benefit against costs, further informed by patient preferences and societal values. Given the greater efficiency with which IMRT can now be delivered, if societal costs can be aligned more closely with actual planning and delivery costs, use of IMRT may indeed be preferred, in light of the recent Korean trial and the findings of the present study. Together, these studies offer strong evidence of a modest incremental benefit of inverse-planned IMRT, even compared with high-quality 3D CRT and delivered in the setting of moderate hypofractionation, which itself reduces the likelihood of toxicity. That said, rates of extremely severe toxicity, such as grade 3 events or those requiring treatment breaks, are rare regardless of technique in this sample.

Current consensus guidelines emphasize the utility of standardizing dosimetric goals in treatment planning. Further research is necessary to understand the dosimetric differences between the IMRT and 3D plans in this data set that may have led to the difference in toxicity observed in this study. Prior work has suggested that limiting V105% may be helpful in larger breasted patients treated with hypofractionation. In addition, dose to the skin and/or to the superficial rind of tissue closest to skin surface may be important and can be more closely controlled with inverse planning. Additional studies to define criteria for optimizing treatment planning based on the rich dosimetric information available through the MROQC collaborative are now under way. Particularly if the societal costs of delivering 3D CRT and IMRT remain meaningfully different, such work will be important to help guide selection of patients in whom dosimetric goals can be met using 3D CRT and those

**Fig. 4.** Forest plot of multivariable model of acute toxicity among patients treated with hypofractionation. This model uses the inverse probability of treatment weighted sample of patients treated with hypofractionation to consider the binary outcome of acute toxicity (having moist desquamation or moderate or severe pain). It uses the logit link for the binomial distribution to determine the association with treatment technique, estimated as odds ratios, after adjustment for all covariates and including the institution of treatment as a random effect. **Abbreviations:** 3D CRT = 3-dimensional conformal radiation therapy; BMI = body mass index; IMRT = intensity modulated radiation therapy; ITPW = inverse probability of treatment weighting.
in whom the use of IMRT is necessary. As Vicini et al noted, “We must move away from the notion of IMRT as a modality and focus on what it allows us to do.”

Our study has numerous strengths, including its inclusion of multiple centers with varying rates of IMRT use, a diverse patient population and real-world data reported by both clinicians and patients along with treatment planning information with greater detail than available through any other registry of this scale, to our knowledge. However, it also has limitations. Causal inference from observational data is notoriously fraught with difficulties, and although we applied sophisticated analytical techniques to minimize the effect of treatment selection bias, unmeasured confounding factors may still have exerted influence on our results. However, given the consistent findings of the one randomized trial to investigate this important question that was recently reported from Korea and the low likelihood that such trials will ever be conducted in the United States, we believe our findings represent key real-world evidence to guide clinical practice and policies in this context in the United States. Our study represented real-world practice, but this also resulted in nontrivial amounts of missing data, which may also introduce biases. Where patient reports of pain were missing, we relied on physician reports, which are not as sensitive. In addition, our analyses were based on patients treated in centers in the state of Michigan. Our findings should not be extrapolated to settings where the quality of radiation therapy care diverges substantially from that delivered in Michigan or where IMRT approaches differ substantially or are defined differently from those used by centers in the current study.

Our study focused exclusively on acute toxicity. Although late soft tissue effects such as fibrosis in this setting may well be consequential to severe acute toxicity, they may also develop unexpectedly. Moreover, long-term outcomes, including disease control and late toxicities of other organs that may receive incidental irradiation, are important subjects for future research. It may be particularly important to use IMRT techniques that limit the amount of low-dose RT to the lungs and contralateral breast because this exposure may have consequences for late toxicity and second malignancy. Our study focused on the use of IMRT to reduce skin toxicity in node-negative patients; however, inverse-planned IMRT may also be used to reduce dose to critical normal structures, including the heart. On the other hand, certain IMRT techniques may actually increase dose to underlying organs, including the heart and lungs, and an improvement in acute toxicity at the cost of higher doses to such regions would not be an appropriate trade-off; further dosimetric analyses are ongoing to evaluate that concern. With different dose fractionation schemas used, it is also relevant to investigate toxicity as a function of the biologically equivalent dose in 2 Gy fractions. Further research is necessary to evaluate the effect of IMRT in the setting of node-positive disease for the purposes of cardiac avoidance.

Conclusions

What have we learned from this large-scale, prospective observational analysis of comparative effectiveness of IMRT versus 3DCRT in the management of breast cancer? First, there appears to be a modest but significant benefit in the reduction of acute toxicity from the use of more complex forms of IMRT compared with 3DCRT in the overall patient population as treated in real-world settings in Michigan, regardless of whether conventional fractionation or hypofractionation is employed. Second, choice of fractionation affects acute toxicity far more than choice of technique. These observations have important implications. Creative efforts to promote appropriate use of moderate hypofractionation remain most essential, particularly given early observations of slow uptake of that approach. Interestingly, IMRT was adopted more quickly—even before evidence of its benefit—than hypofractionation. The present study suggests that uptake of both approaches would minimize rates of acute toxicity, but clinical policy must consider differences in costs as well. Further research is necessary to define dosimetric goals to determine which patients require IMRT and to optimize patient outcomes and standardize techniques in this context. Further research is also necessary to evaluate long-term outcomes and to define the role of IMRT in patients being treated with regional nodal irradiation.

References


