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Comparative Effectiveness Analysis of 3D-Conformal Radiotherapy versus Intensity Modulated Radiotherapy (IMRT) in a Prospective Multicenter Cohort of Breast Cancer Patients

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Data Availability

Data are owned by the local collaborating sites and therefore MROQC is not permitted to share the data used for this study.

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ABSTRACT

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

Methods and Materials: Using prospective data regarding patients receiving adjuvant whole breast RT without nodal irradiation at 23 institutions from 2011-2018, we compared 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 (IPTW), adjusting for treatment facility as a random effect.

Results: Of 1,185 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; of 580 treated with inverse-planned IMRT, 245 (42.2%) did. Of 1,296 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; of 623 treated with inverse-planned IMRT, 164 (26.3%) did. On multivariable analysis with IPTW, the odds ratio for acute toxicity after inverse-planned IMRT versus 3DCRT was 0.64 (95% CI, 0.45-0.91) with conventional fractionation and 0.41 (95% CI, 0.26-0.65) with hypofractionation.

Conclusions: This large, prospective, multicenter comparative effectiveness study found a significant benefit from inverse-planned IMRT compared to 3DCRT in reducing acute toxicity of breast radiotherapy. Future research should identify the dosimetric differences that mediate this association and evaluate cost-effectiveness.

Introduction:

The term "intensity modulated radiotherapy" or "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 dosimetrist, or more complex (Supplemental Appendix Figure A1). 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, as compared to 2-dimensional treatment planning.[1,2] However, the IMRT approach evaluated in those studies was frequently forward-planned and similar to what many U.S. centers would call 3-dimensional conformal radiotherapy (3DCRT), rather than IMRT, which in the U.S. has most frequently been defined by insurers as treatment involving the division of at least one 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[3,4]—stakeholders have wondered whether more complex IMRT is necessary to reduce toxicity or whether perhaps the use of 3DCRT might suffice. Unfortunately, given the rapid adoption of IMRT technology,[5] a randomized trial directly comparing 3DCRT to more sophisticated forms of IMRT has not been feasible in the US, although a Korean trial recently reported findings of reduced toxicity with IMRT among patients receiving conventionally fractionated breast radiotherapy.[6] Over the past decade, practice patterns have diverged considerably amongst institutions,[7,8,9] and comparison of these two approaches in real-world practice in the US remains a key question that must be answered to ensure appropriate direction of clinical practice.

Therefore, in 2011, with funding from [Anonymized for Review], we initiated a multicenter collaborative quality initiative, the [Anonymized for Review], with a primary objective of evaluating the impact of IMRT in patients with breast cancer and lung cancer. This manuscript 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.

Methods:

Data Collection and Sample

We obtained IRB approval to collect prospectively a rich array of treatment planning data and physician assessments for all eligible patients treated at [Anonymized for Review] member institutions with whole breast radiotherapy, as part of a quality improvement initiative.[10,11] Eligible patients were those women being treated with adjuvant whole breast radiotherapy for non-metastatic, unilateral breast cancer without having breast implants at an [Anonymized for Review]-participating institution. We also obtained IRB approval to collect patient-reported data from those patients who consented to participate in weekly surveys while on treatment.

Our sample derived from the 8,228 breast cancer patients meeting analytic eligibility criteria who received adjuvant whole breast RT at 24 institutions participating in the [Anonymized for Review] between November 2011 and September 2018. Analytic 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 (DVH) for the breast. We

required that all patients included in the analytic 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 one institution from the analytic sample, with the smallest remaining institutional contribution 22 cases and the largest contribution 471.

We considered 5,167 cases in total: 2,539 patients treated with conventional fractionation and 2,628 treated with hypofractionation (defined as utilizing a dose per fraction greater than 2.0 Gy)[12]. Figure 1 details the flow of patients into the analytic sample.

Measures

The primary, pre-defined 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,[13,14] in 3,947 cases (76.4%), and physician-reported using the CTCAE scale in the 1,220 (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 two 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 Figure 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, BMI, chemotherapy receipt, whether institution was an academic center (trains residents or fellows), separation distance (the distance separating the entry points of typical tangential beams at 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 two groups had substantially different rates of acute toxicity.[15,16] 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, in order 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 above. 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.[17] 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 in order 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 two 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 two 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 three treatment groups.

Results:

Table 1 shows 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 between 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 (see Supplemental Appendix Table A1).

Of the 1,185 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; of 580 treated with inverse-planned IMRT, 245 (42.2%) did. Of 1,296 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; of 623 treated with inverse-planned IMRT, 164 (26.3%) did. As noted in the methods, 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, 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 2 shows the results of models, including a crude unadjusted comparison and then three 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 the table, 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 as compared to 3DCRT was 0.64 (95% CI, 0.45-0.91) in patients receiving conventional fractionation and 0.41 (95% CI, 0.26-0.65) in patients receiving hypofractionation. On sensitivity analysis that subdivided the inverse-planned cases into two subgroups based on number of segments, findings were consistent in both magnitude and direction when each of

these subgroups was compared to 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 0.7% of patients treated with 3DCRT, 0.2% of those treated with highly segmented forward-planned IMRT, and 0% of those treated with inverse-planned IMRT (p=0.026). For conventionally fractionated cases, CTCAE Grade 3 radiation dermatitis occurred in 2.4% of pts treated with 3DCRT, 1.8% of those treated with highly segmented forward-planned IMRT, and 1.6% of those treated with IMRT (p=0.443). 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=0.053). 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-planned IMRT, and 3.6% of those treated with IMRT (p=0.003). 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 as compared to 3DCRT in adjuvant whole breast radiotherapy. 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 radiotherapy. 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.[18] 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 (OR on multivariable modeling 0.65; p= .038) or skin telangiectasia (OR, 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.[19,20] 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 3D-CRT (because their insurers refused coverage for IMRT). In that study, the delivery was a combination of 3D 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%).[20]

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. 27.8%; p = 0.009). 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[21,22] and more complex but efficient approaches.[23] Nevertheless, differences in fee schedules for reimbursement of radiation therapy using different techniques have led both to concerns about the possible *over*use 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 *under*use of IMRT, due to a desire to responsibly steward resources.[24] 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, whether to recommend widespread use of more complex forms of IMRT for whole breast irradiation requires 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,

which together offer strong evidence of a modest incremental benefit of inverse-planned IMRT, even when compared to high quality 3DCRT and even when 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 quite rare regardless of technique in this sample.

Current consensus guidelines emphasize the utility of standardizing dosimetric goals in treatment planning.[25] Further research is necessary to understand the dosimetric differences between the IMRT and 3D plans in this dataset 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.[26] In addition, dose to the skin[27] and/or to the superficial rind of tissue closest to skin surface may be important and can be more closely controlled with inverse planning.[28] Additional studies to define criteria for optimizing treatment planning based on the rich dosimetric information available through the [Anonymized for Review] collaborative are now underway. Particularly if the societal costs of delivering 3DCRT and IMRT remain meaningfully different, such work will be especially important to help guide selection of patients in whom dosimetric goals can be met using 3DCRT and those 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."[23]

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,[29,30] and although we applied sophisticated analytic techniques to minimize the impact 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 non-trivial 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 [Anonymized for Review]. Our findings should not be extrapolated to settings where the quality of radiotherapy care diverges substantially from that which is delivered in [Anonymized for Review] or where IMRT approaches differ substantially or are defined differently from those used by centers in the current study.

Of note, 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 utilize IMRT techniques that limit the amount of low-dose RT to the lungs and contralateral breast,[31] as this exposure may have consequences for late toxicity and second malignancy.[32] 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.[33,34,35,36] On the other hand, certain techniques of IMRT 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 tradeoff; 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 impact of IMRT in the setting of node-positive disease for the purposes of cardiac avoidance.[4]

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 as compared to 3DCRT in the overall patient population as treated in real-world settings in [Anonymized for Review], 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,[11,37,38] particularly given early observations of slow uptake of that approach.[39,40] Interestingly, IMRT was adopted more quickly—even prior to evidence of its benefit—than hypofractionation.[5] 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.[41,42]

Figure Legends

Figure 1: Flow of patients into the study sample
This figure shows how patients were selected for inclusion in the analytic sample.

Figure 2: Distribution of the use of the treatment techniques by enrolling site.
This figure shows the use of the three forms of treatment (3DCRT, highly-segmented forward-planned IMRT, and inverse-planned IMRT) in patients treated with each fractionation approach.

Figure 3: Forest Plot of Multivariable Model of Acute Toxicity Among Patients Treated with Conventional Fractionation
Using the inverse-probability-of-treatment-weighted sample of patients treated with conventional fractionation, this model considers the binary outcome of acute toxicity (having moist desquamation or moderate or severe pain) using the logit link for the binomial distribution in order 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.

Figure 4: Forest Plot of Multivariable Model of Acute Toxicity Among Patients Treated with Hypofractionation.
Using the inverse-probability-of-treatment-weighted sample of patients treated with hypofractionation, this model considers the binary outcome of acute toxicity (having moist desquamation or moderate or severe pain) using the logit link for the binomial distribution in order 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.

Table 1a: Sample characteristics

Conventionally Fractionated (N=2539)					
Variable/Level	**Statistics**	**Total Population**	**3DCRT (N=1185)**	**Highly-Segmented Forward Planned (N=774)**	**Inverse-Planned IMRT (N=580)**
Age (years):	Mean (SD)	58.5 (10.47)	58.41 (10.42)	59.15 (10.35)	57.85 (10.71)
Race: White	N (%)	1938 (76.33)	992 (83.71)	495 (63.95)	451 (77.76)
Black	N (%)	465 (18.31)	144 (12.15)	244 (31.52)	77 (13.28)
Other	N (%)	136 (5.36)	49 (4.14)	35 (4.52)	52 (8.97)
Hypertension: No	N (%)	1500 (59.08)	749 (63.21)	416 (53.75)	335 (57.76)
Yes	N (%)	1039 (40.92)	436 (36.79)	358 (46.25)	245 (42.24)
Diabetes: No	N (%)	2188 (86.18)	1030 (86.92)	653 (84.37)	505 (87.07)
Yes	N (%)	351 (13.82)	155 (13.08)	121 (15.63)	75 (12.93)
Smoking Status: Never	N (%)	1476 (58.13)	707 (59.66)	430 (55.56)	339 (58.45)
Former	N (%)	758 (29.85)	354 (29.87)	235 (30.36)	169 (29.14)
Current	N (%)	305 (12.01)	124 (10.46)	109 (14.08)	72 (12.41)
Hormone therapy: Missing	N (%)	26 (1.02)	19 (1.60)	3 (0.39)	4 (0.69)
No	N (%)	909 (35.80)	408 (34.43)	288 (37.21)	213 (36.72)
Yes	N (%)	1604 (63.17)	758 (63.97)	483 (62.40)	363 (62.59)
Chemotherapy: Missing	N (%)	13 (0.51)	11 (0.93)	2 (0.26)	
No	N (%)	1632 (64.28)	794 (67.00)	476 (61.50)	362 (62.41)
Yes	N (%)	894 (35.21)	380 (32.07)	296 (38.24)	218 (37.59)
Group Stage: 0	N (%)	579 (22.80)	293 (24.73)	167 (21.58)	119 (20.52)
1	N (%)	1336 (52.62)	616 (51.98)	418 (54.01)	302 (52.07)
2	N (%)	612 (24.10)	270 (22.78)	186 (24.03)	156 (26.90)
3	N (%)	12 (0.47)	6 (0.51)	3 (0.39)	3 (0.52)
Separation Distance (cm):	Mean (SD)	23.21 (3.92)	22.69 (3.82)	24.12 (4.04)	23.07 (3.76)
BMI Category: Underweight/Normal <25	N (%)	622 (24.50)	318 (26.84)	146 (18.86)	158 (27.24)
Overweight 25-<30	N (%)	673 (26.51)	308 (25.99)	193 (24.94)	172 (29.66)
Obesity I 30-<35	N (%)	580 (22.84)	274 (23.12)	174 (22.48)	132 (22.76)
Obesity II 35-<40	N (%)	357 (14.06)	158 (13.33)	134 (17.31)	65 (11.21)
Obesity III >40	N (%)	307 (12.09)	127 (10.72)	127 (16.41)	53 (9.14)
Breast total volume (cc):	Mean (SD)	1194.51 (832.46)	1113.06 (599.38)	1340.9 (1118.39)	1165.57 (768.17)
D50 Breast (Gy):	Mean (SD)	51.23 (3.55)	51.45 (3.25)	51.59 (3.53)	50.32 (4.00)
Treatment Facility Academic: No	N (%)	1726 (67.98)	958 (80.84)	505 (65.25)	263 (45.34)
Yes	N (%)	813 (32.02)	227 (19.16)	269 (34.75)	317 (54.66)

Table 1b: Sample characteristics (continued/part 2 of table)

Hypofractionated (N=2628)					
Variable/Level	**Statistics**	**Total Population**	**3DCRT (N=1296)**	**Highly-Segmented Forward-Planned (N=709)**	**Inverse-Planned IMRT (N=623)**
Age (years):	Mean (SD)	62.53 (10.03)	62.27 (9.82)	63.7 (10.04)	61.72 (10.34)
Race: White	N (%)	2094 (79.68)	1157 (89.27)	443 (62.48)	494 (79.29)
Black	N (%)	395 (15.03)	84 (6.48)	232 (32.72)	79 (12.68)
Other	N (%)	139 (5.29)	55 (4.24)	34 (4.80)	50 (8.03)
Hypertension: No	N (%)	1729 (65.79)	904 (69.75)	424 (59.80)	401 (64.37)
Yes	N (%)	899 (34.21)	392 (30.25)	285 (40.20)	222 (35.63)
Diabetes: No	N (%)	2342 (89.12)	1180 (91.05)	600 (84.63)	562 (90.21)
Yes	N (%)	286 (10.88)	116 (8.95)	109 (15.37)	61 (9.79)
Smoking Status: Never	N (%)	1502 (57.15)	770 (59.41)	391 (55.15)	341 (54.74)
Former	N (%)	829 (31.54)	396 (30.56)	225 (31.73)	208 (33.39)
Current	N (%)	297 (11.30)	130 (10.03)	93 (13.12)	74 (11.88)
Hormone therapy: Missing	N (%)	27 (1.03)	14 (1.08)	4 (0.56)	9 (1.44)
No	N (%)	843 (32.08)	442 (34.10)	188 (26.52)	213 (34.19)
Yes	N (%)	1758 (66.89)	840 (64.81)	517 (72.92)	401 (64.37)
Chemotherapy: Missing	N (%)	7 (0.27)	5 (0.39)	2 (0.28)	
No	N (%)	2206 (83.94)	1065 (82.18)	606 (85.47)	535 (85.87)
Yes	N (%)	415 (15.79)	226 (17.44)	101 (14.25)	88 (14.13)
Group Stage: 0	N (%)	596 (22.68)	260 (20.06)	168 (23.70)	168 (26.97)
1	N (%)	1567 (59.63)	821 (63.35)	425 (59.94)	321 (51.52)
2	N (%)	462 (17.58)	213 (16.44)	115 (16.22)	134 (21.51)
3	N (%)	3 (0.11)	2 (0.15)	1 (0.14)	
Separation Distance (cm):	Mean (SD)	22.54 (3.50)	21.98 (3.22)	23.26 (3.49)	22.87 (3.88)
BMI Category: Underweight/Normal <25	N (%)	728 (27.70)	398 (30.71)	140 (19.75)	190 (30.50)
Overweight 25-<30	N (%)	863 (32.84)	457 (35.26)	214 (30.18)	192 (30.82)
Obesity I 30-<35	N (%)	576 (21.92)	264 (20.37)	180 (25.39)	132 (21.19)
Obesity II 35-<40	N (%)	275 (10.46)	106 (8.18)	111 (15.66)	58 (9.31)
Obesity III >40	N (%)	186 (7.08)	71 (5.48)	64 (9.03)	51 (8.19)
Breast total volume (cc):	Mean (SD)	1038.83 (561.61)	944.86 (479.10)	1147.88 (592.33)	1110.2 (646.37)
D50 Breast (Gy):	Mean (SD)	45.18 (2.39)	44.76 (2.23)	45.55 (2.59)	45.65 (2.33)
Treatment Facility Academic: No	N (%)	1553 (59.09)	1075 (82.95)	398 (56.14)	80 (12.84)
Yes	N (%)	1075 (40.91)	221 (17.05)	311 (43.86)	543 (87.16)

Table 2: Overview of models of acute toxicity by RT technique

	Proportion Composite Acute Radiation-induced toxicity			Odd Ratios and 95% Confidence Intervals	
Models/Population	**(1) 3DCRT (forward-planned, <5 segments)**	**(2) Highly-segmented forward-planned IMRT (forward planned, 5+ segments)**	**(3) Inverse-planned IMRT**	**Group 2 vs 1**	**Group 3 vs 1**
Conventional Fractionation					
Unadjusted	0.5485	0.5917	0.4224	1.19[0.99, 1.43]	0.60[0.49, 0.74]
IPTW Adjusted Only	0.5759	0.5584	0.4238	0.93[0.76, 1.13]	0.54[0.43, 0.69]
IPTW Adjusted + Covariates	0.6046	0.5721	0.4410	0.87[0.71, 1.08]	0.52[0.40, 0.66]
IPTW Adjusted + Covariates + Hospital (Random Effect)	0.5732	0.6034	0.4626	1.13[0.88, 1.46]	0.64[0.45, 0.91]
Hypofractionation					
Unadjusted	0.3333	0.3202	0.2632	0.94[0.77, 1.15]	0.71[0.58, 0.88]
IPTW Adjusted Only	0.3522	0.2902	0.2139	0.75[0.59, 0.95]	0.50[0.33, 0.77]
IPTW Adjusted + Covariates	0.3485	0.2799	0.2092	0.73[0.57, 0.93]	0.49[0.33, 0.74]
IPTW Adjusted + Covariates + Hospital (Random Effect)	0.3637	0.2999	0.1894	0.75[0.54, 1.03]	0.41[0.26, 0.65]

Figure 1: Flow of patients into the study sample

This figure shows how patients were selected for inclusion in the analytic sample.

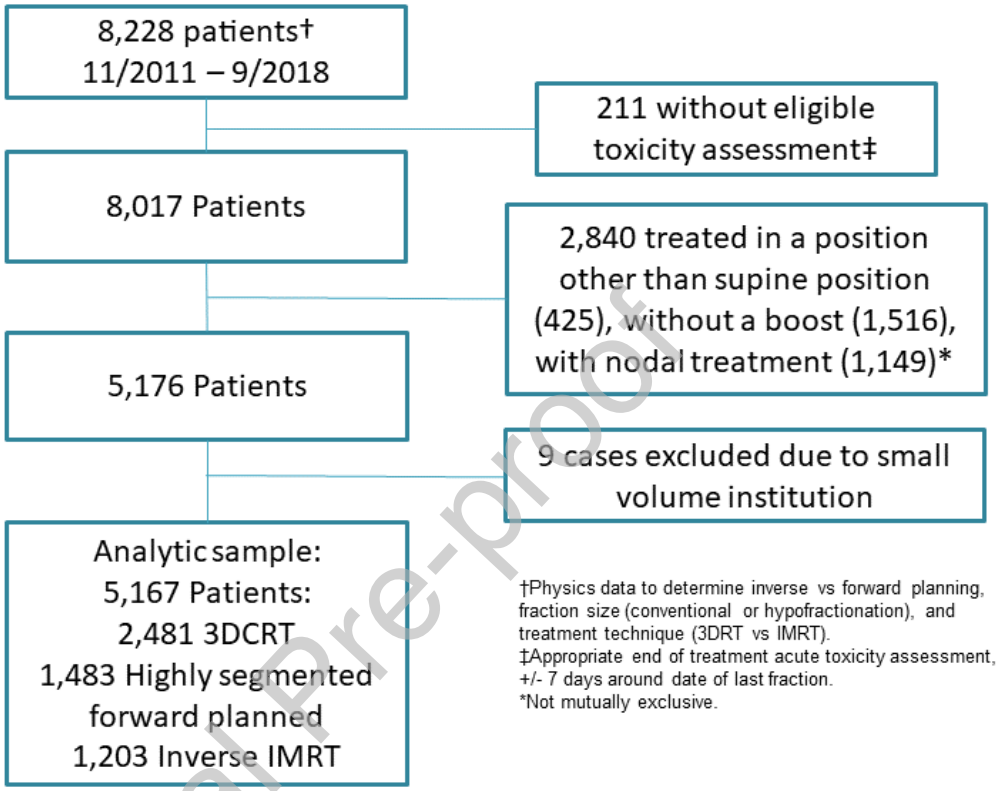


Figure 2: Distribution of the use of the treatment techniques by enrolling site.

This figure shows the use of the three forms of treatment (3DCRT, highly-segmented forward-planned IMRT, and inverse-planned IMRT) in patients treated with each fractionation approach.

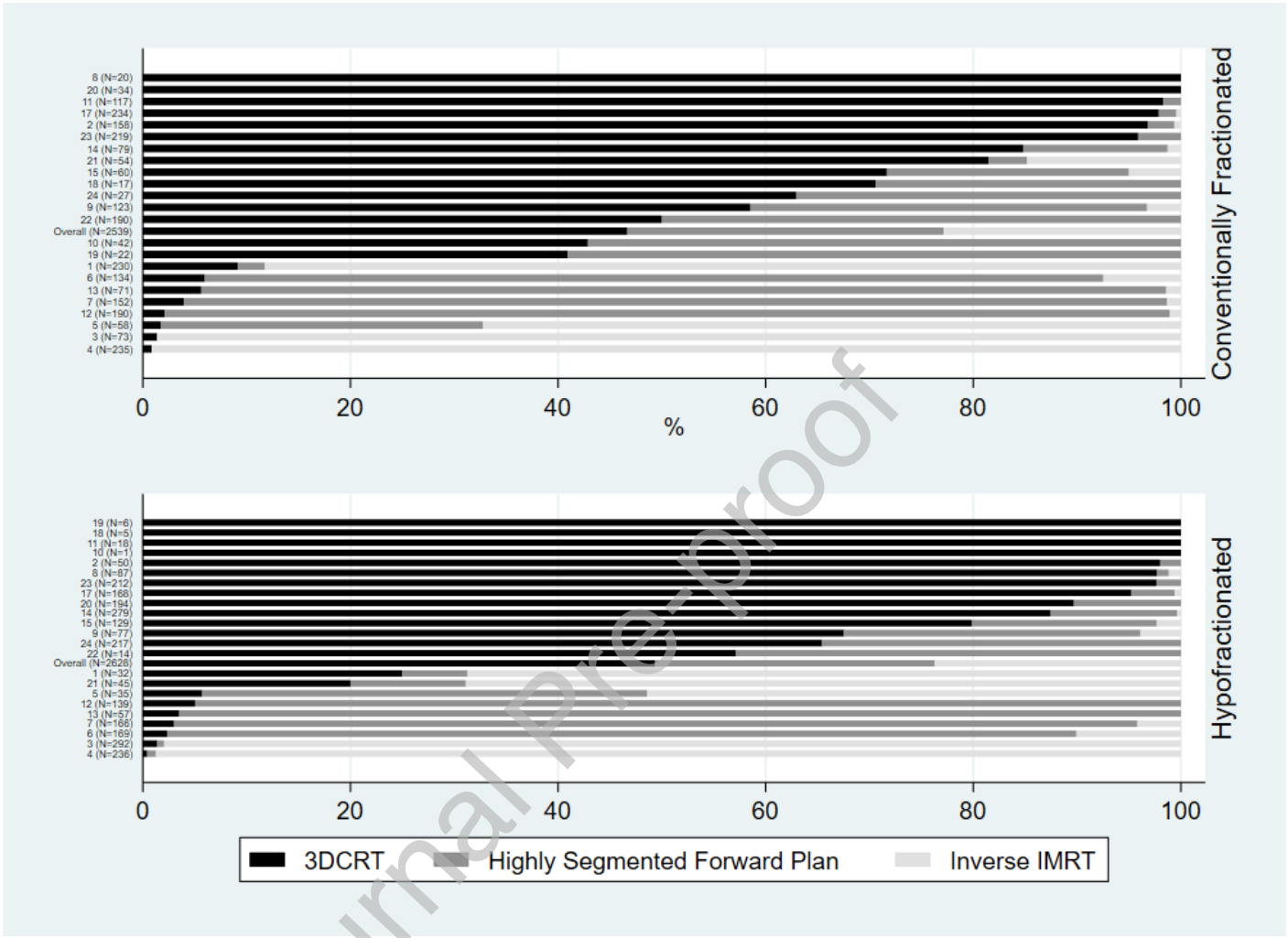
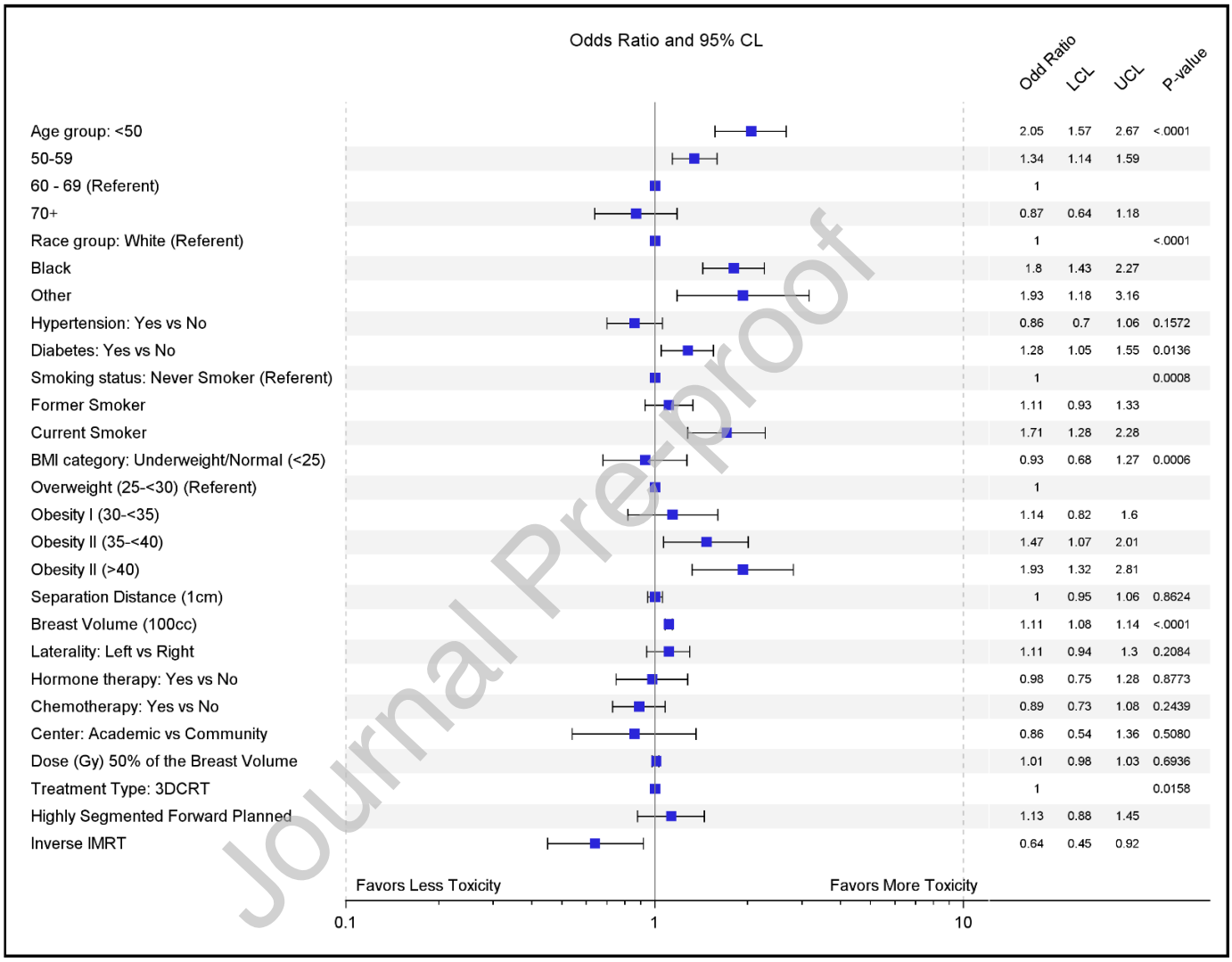


Figure 3: Forest Plot of Multivariable Model of Acute Toxicity Among Patients Treated with Conventional Fractionation.

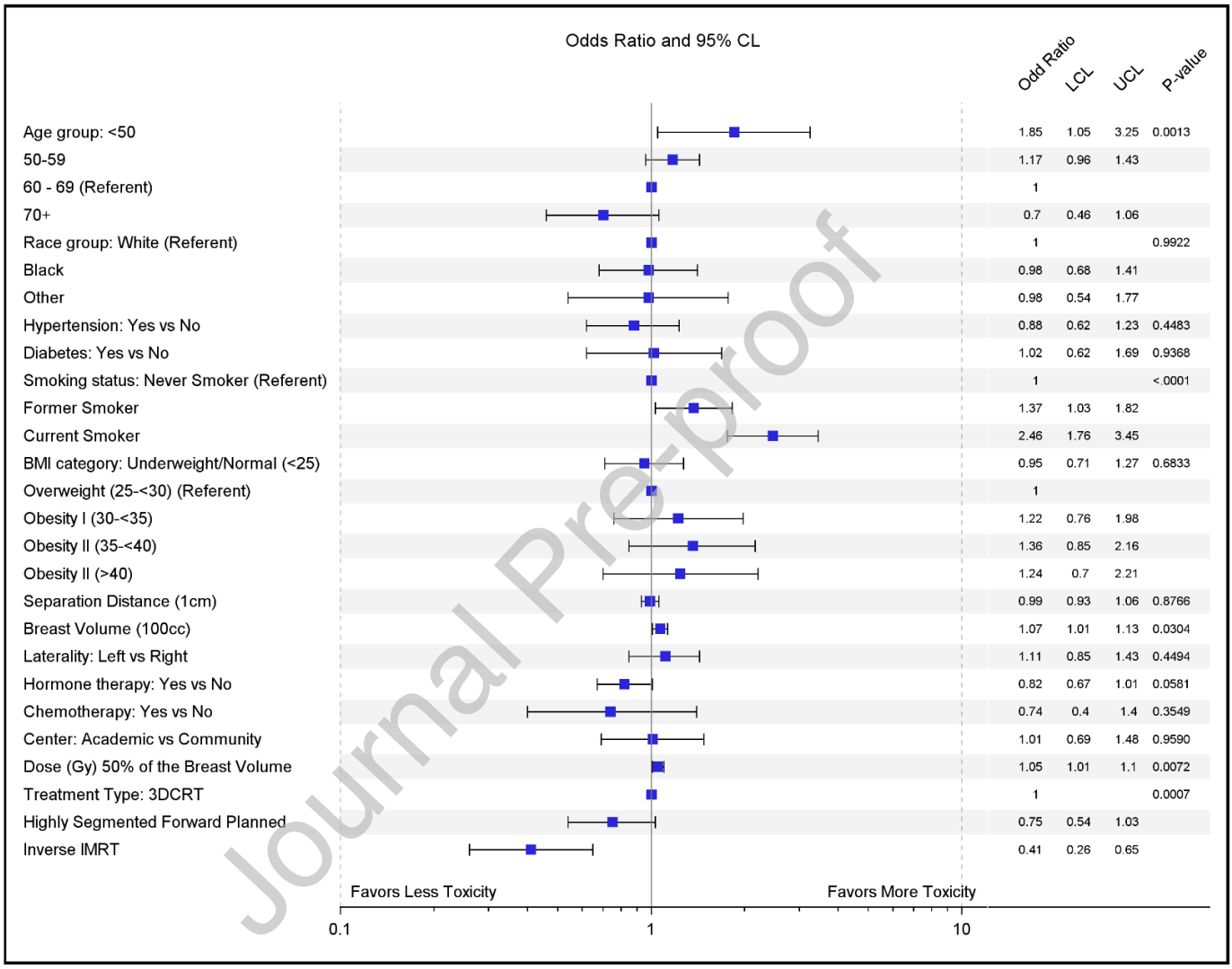
Using the inverse-probability-of-treatment-weighted sample of patients treated with conventional fractionation, this model considers the binary outcome of acute toxicity (having moist desquamation or moderate or severe pain) using the logit link for the binomial distribution in order to determine the association with treatment technique, estimated as odds ratios, after adjustment for all covariates and including the institution of treatment as a random effect.



* Model uses IPTW, covariate adjustment, and includes hospital site as random effect.

Figure 4: Forest Plot of Multivariable Model of Acute Toxicity Among Patients Treated with Hypofractionation.

Using the inverse-probability-of-treatment-weighted sample of patients treated with hypofractionation, this model considers the binary outcome of acute toxicity (having moist desquamation or moderate or severe pain) using the logit link for the binomial distribution in order 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.



*Model uses IPTW, covariate adjustment, and includes hospital site as random effect.

References

[1] Mukesh M, Barnett G, Wilkinson J, et al: Randomized Controlled Trial of Intensity-Modulated Radiotherapy for Early Breast Cancer: 5-Year Results Confirm Superior Overall Cosmesis. *J Clin Oncol* 2013;31(36):4488–4495.

[2] Pignol J-P, Olivotto I, Rakovitch E, et al: A Multicenter Randomized Trial of Breast Intensity-Modulated Radiation Therapy to Reduce Acute Radiation Dermatitis. *J Clin Oncol* 2008;26(13):2085–2092.

[3] Centers for Medicare & Medicaid Services: Fee Schedules - General Information. Page last updated: 03-02-2021. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/FeeScheduleGenInfo.

[4] Jagsi R, Griffith KA, Moran JM, et al: A Randomized Comparison of Radiation Therapy Techniques in the Management of Node-Positive Breast Cancer: Primary Outcomes Analysis. *Int J Radiat Oncol Biol Phys* 2018;101(5):1149–1158.

[5] Smith BD, Pan I-W, Shih Y-CT, et al: Adoption of intensity-modulated radiation therapy for breast cancer in the United States. *J Natl Cancer Inst* 2011;103(10):798–809.

[6] Choi KH, Ahn SJ, Jeong JU, et al. Postoperative radiotherapy with intensity-modulated radiation therapy versus 3-dimensional conformal radiotherapy in early breast cancer: A randomized clinical trial of KROG 15-03. *Radiother Oncol.* 2021;154:179-186.

[7] [Anonymized for Review]

[8] Roberts KB, Soulos PR, Herrin J, et al: The adoption of new adjuvant radiation therapy modalities among Medicare beneficiaries with breast cancer: clinical correlates and cost implications. *Int J Radiat Oncol Biol Phys* 2013;85(5):1186–1192.

[9] Wang EH, Mougalian SS, Soulos PR, et al: Adoption of intensity modulated radiation therapy for early-stage breast cancer from 2004 through 2011. *Int J Radiat Oncol Biol Phys* 2015;91(2):303–311.

[10] [Anonymized for Review]

[11] [Anonymized for Review]

[12] [Anonymized for Review]

[13] Cleeland CS, Ryan KM: Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap* 1994;23(2):129–138.

[14] Jagsi R, Griffith KA, Vicini F, et al: Toward Improving Patients' Experiences of Acute Toxicity From Breast Radiotherapy: Insights From the Analysis of Patient-Reported Outcomes in a Large Multicenter Cohort. *J Clin Oncol* 202;38(34):4019–4029.

[15] Jagsi R, Griffith KA, Boike TP, et al: Differences in the Acute Toxic Effects of Breast Radiotherapy by Fractionation Schedule: Comparative Analysis of Physician-Assessed and Patient-Reported Outcomes in a Large Multicenter Cohort. *JAMA Oncol* 2015;1(7):918.

[16] Arsenault J, Parpia S, Goldberg M, et al: Acute Toxicity and Quality of Life of Hypofractionated Radiation Therapy for Breast Cancer. *Int J Radiat Oncol Biol Phys* 2020;107(5):943–948.

[17] Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-3679.

[18] Harsolia A, Kestin L, Grills I, et al: Intensity-Modulated Radiotherapy Results in Significant Decrease in Clinical Toxicities Compared with Conventional Wedge-Based Breast Radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;8(5):1375–1380.

[19] McDonald MW, Godette KD, Butker EK, et al: Long-Term Outcomes of IMRT for Breast Cancer: A Single-Institution Cohort Analysis. *Int J Radiat Oncol Biol Phys* 2008;72(4):1031–1040.

[20] Hardee ME, Raza S, Becker SJ, et al: Prone Hypofractionated Whole-Breast Radiotherapy Without a Boost to the Tumor Bed: Comparable Toxicity of IMRT Versus a 3D Conformal Technique. *Int J Radiat Oncol Biol Phys* 2012;82(3):e415–e423.

[21] Kestin LL, Sharpe MB, Frazier RC, et al: Intensity modulation to improve dose uniformity with tangential breast radiotherapy: initial clinical experience. *Int J Radiat Oncol Biol Phys* 2000;48(5):1559-1568.

[22] Vicini FA, Sharpe M, Kestin L, et al: Optimizing breast cancer treatment efficacy with intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;54(5):1336–1344.

[23] Farace P, Zucca S, Solla I, et al: Planning Hybrid Intensity Modulated Radiation Therapy for Whole-breast Irradiation. *Int J Radiat Oncol Biol Phys* 2012;84(1):e115–e122.

[24] Vicini F, Sharpe M, Kestin L, et al: The use of intensity modulated radiation therapy in the treatment of breast cancer: evolving definition, misdirected criticism, and untoward effects. *Int J Radiat Oncol Biol Phys*. 2004;58(5):1642-1644.

[25] Smith BD, Bellon JR, Blitzblau R, et al: Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol* 2018;8(3):145–152.

[26] Patel AK, Ling DC, Richman AH, et al: Hypofractionated Whole-Breast Irradiation in Large-Breasted Women—Is There a Dosimetric Predictor for Acute Skin Toxicities? *Int J Radiat Oncol Biol Phys* 2019;103(1):71–77.

[27] Pasquier D, Bataille B, Le Tinier F, et al: Correlation between toxicity and dosimetric parameters for adjuvant intensity modulated radiation therapy of breast cancer: a prospective study. *Sci Rep* 2021;11(1):3626.

[28] Saibishkumar EP, MacKenzie MA, Severin D, et al: Skin-Sparing Radiation Using Intensity-Modulated Radiotherapy After Conservative Surgery in Early-Stage Breast Cancer: A Planning Study. *Int J Radiat Oncol Biol Phys* 2008(2);70:485–491.

[29] McGale P, Cutter D, Darby SC, et al: Can Observational Data Replace Randomized Trials? *J Clin Oncol* 2016(27);4:3355–3357.

[30] Jagsi R, Bekelman JE, Chen A, et al: Considerations for Observational Research Using Large Data Sets in Radiation Oncology. *Int J Radiat Oncol Biol Phys* 2014;90(1):11–24.

[31] Beckham WA, Popescu CC, Patenaude VV, et al: Is Multibeam IMRT Better Than Standard Treatment for Patients with Left-Sided Breast Cancer? *Int J Radiat Oncol Biol Phys* 2007;69(3):918–924.

[32] Hall EJ, Wuu C-S: Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys* 2003;56(1):83–88.

[33] Jagsi R, Moran J, Marsh R, et al: Evaluation of four techniques using intensity-modulated radiation therapy for comprehensive locoregional irradiation of breast cancer. *Int J Radiat Oncol Biol Phys* 2010;78(5):1594–1603.

[34] Ho AY, Ballangrud A, Li G, et al: Long-Term Pulmonary Outcomes of a Feasibility Study of Inverse-Planned, Multibeam Intensity Modulated Radiation Therapy in Node-Positive Breast Cancer Patients Receiving Regional Nodal Irradiation. *Int J Radiat Oncol Biol Phys* 2019;103(5):1100–1108.

[35] Bazan JG, Healy E, Beyer S, et al: Clinical Effectiveness of an Adaptive Treatment Planning Algorithm for Intensity Modulated Radiation Therapy Versus 3D Conformal Radiation Therapy for Node-Positive Breast Cancer Patients Undergoing Regional Nodal Irradiation/Postmastectomy Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2020;108(5):1159–1171.

[36] Lohr F, El-Haddad M, Dobler B, et al: Potential Effect of Robust and Simple IMRT Approach for Left-Sided Breast Cancer on Cardiac Mortality. *Int J Radiat Oncol Biol Phys* 2009;74(1):73–80.

[37] Ganju RG, TenNapel M, Chen AM, et al: Impact of Peer Review on Use of Hypofractionated Regimens for Early-Stage Breast Cancer for Patients at a Tertiary Care Academic Medical Center and Its Community-Based Affiliates. J*CO Oncol Pract* 2019;15(2):e153–e161.

[38] Rodríguez-Lopéz JL, Ling DC, Heron DE, et al: Lag Time Between Evidence and Guidelines: Can Clinical Pathways Bridge the Gap? *JCO Oncol Pract* 2019;15(3):e195–e201.

[39] Woodward SG, Varshney K, Anne PR, et al: Trends in Use of Hypofractionated Whole Breast Radiation in Breast Cancer: An Analysis of the National Cancer Database. *Int J Radiat Oncol Biol Phys* 2021;109(2):449–457.

[40] Jagsi R, Falchook AD, Hendrix LH, et al: Adoption of Hypofractionated Radiation Therapy for Breast Cancer After Publication of Randomized Trials. I*nt J Radiat Oncol Biol Phys* 2014;90(5):1001–1009.

[41] Whelan TJ, Olivotto IA, Parulekar WR, et al: Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med* 2015;373(4):307–316.

[42] Poortmans PM, Collette S, Kirkove C, et al: Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. *N Engl J Med* 2015;373(4):317–327.