Advances in Radiation Oncology (2024) 9, 101629

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Microboost in Localized Prostate Cancer: Analysis of a Statewide Quality Consortium

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Received 2 May 2024; accepted 5 September 2024

Purpose: Prospective trials have reported isotoxicity and improved oncologic outcomes with external beam radiation therapy (EBRT) microboost to a dominant intraprostatic lesion. There is often variability in the rate of adoption of new treatments, and current microboost practice patterns are unknown. We leveraged prospectively collected data from the multicenter Michigan Radiation Oncology Quality Consortium to understand the current state of microboost usage for localized prostate cancer.

Materials and Methods: Men with intermediate- and high-risk prostate adenocarcinoma treated with curative-intent radiation between October, 26, 2020, and June, 26, 2023, were included across 26 centers. Demographic-, tumor-, and treatment-related data along with DICOM files were prospectively collected. Microboost intent was prospectively documented and DICOM-confirmed. Multivariable analyses were used to evaluate associations with microboost receipt, and mixed-effects modeling evaluated facility-level variation.

Results: Most patients received EBRT without brachytherapy (71%, n = 524/741). Of those, a minority received an EBRT microboost (10%, n = 53/524) at a subset of sites (27%, n = 7/26), without a change in rate over the study period ($P = .62$). Grade group 4/5 (odds ration [OR] = 2.35; 95% confidence interval [CI]: 1.02-5.28), magnetic resonance imaging planning (OR = 6.34; 95%CI: 2.16-27.12), and fiducial marker/rectal spacer placement (OR = 2.59; 95% CI: 1.14-6.70) were associated with microboost use. Significant facility-level variability was present (minimum 0%; 95% CI: 0.0-10.7 to maximum 71%; 95% CI: 55.5-83.2, unadjusted, $P < .0001$). Median boost volume was 20.7cc, and median boost D98% was 94.4 EQD2Gy. Compared with non-microboost cases, intermediate doses to

Sources of support: Michigan Radiation Oncology Quality Consortium is financially supported by Blue Cross Blue Shield of Michigan (BCBSM) and the Blue Care Network of Michigan as part of the BCBSM Value Partnerships Program.

Research data are not authorized to share Michigan Radiation Oncology Quality Consortium (MROQC) data. The data are individually owned by the member institutions of MROQC.

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https://doi.org/10.1016/j.adro.2024.101629

rectum in the microboost cohort were increased (eg, V20Gy [EQD2] of 53.8% vs 36.5%, $P = .03$). However, the proportion exceeding NRG/RTOG bladder/rectal constraints was low and not significantly different between cohorts.

Conclusions: Despite prospective data demonstrating its benefit, EBRT microboost was used within a diverse statewide quality consortium in only 10% of cases at 27% of sites with significant facility-level heterogeneity. Concerted efforts are required to understand current barriers to microboost utilization, and results from trials such as PIVOTALboost (ISRCTN80146950) are eagerly awaited.

Introduction

Definitive radiation therapy is a curative treatment option for men with localized prostate adenocarcinoma. Radiation dose escalation improves outcomes, and different strategies of dose escalation exist. Long-term analysis of RTOG 0126 revealed that whole prostate dose-escalated radiation via external beam radiation therapy (EBRT) resulted in improved local control, decreased distant metastases, and less utilization of salvage therapies in favorable-risk patients.[1] Moreover, the GETUG-AFU 18 trial suggests that dose-escalated EBRT with long-term androgen deprivation improved both prostate cancer-specific and overall survival in unfavorable-risk patients.[2] However, not all dose escalation studies have translated into meaningful differences in metastases or survival,[3-5] and higher radiation dose can result in increased treatment-related toxicity,[1] including late gastrointestinal[6] and/or genitourinary complications.[7]

Advances in imaging and radiation treatment delivery now allow for focal dose escalation to gross intraprostatic disease. Prospective studies have explored the delivery of a simultaneous integrated microboost to multiparametric magnetic resonance imaging (MRI)-defined intraprostatic lesions across a variety of fractionation schemes.[8-10] A microboost strategy is appealing because local failures are often at the initial site of gross disease,[11,12] and an EBRT-delivered boost can be incorporated into clinical practices irrespective of barriers to brachytherapy access.[13] Microboost to gross disease can improve 5-year biochemical endpoints,[8,9] as well as local and regional/distant metastatic failure rates.[14] Importantly, toxicity analyses of EBRT microboost with a variety of fractionations are reassuring and suggest isotoxicity.[8,9,15]

Despite these promising results, there are limited data available regarding the uptake of EBRT microboost in routine practice, and multiple provider concerns about its use may exist.[16] Given the technical expertise required to safely deliver it, we hypothesized that the use of EBRT microboost would be variable. We therefore aimed to characterize both microboost utilization and dosimetry in localized prostate cancer for men treated within a statewide radiation oncology quality consortium.

Methods

Data collection and outcomes

The Michigan Radiation Oncology Quality Consortium (MROQC) is a collaborative quality initiative among a diverse collection of centers across the state, in partnership with Blue Cross Blue Shield of Michigan and Blue Care Network. Participating centers within MROQC prospectively collected deidentified patient and treatment-related data via standardized forms for patients with prostate cancer treated with curative-intent radiation therapy. Eligible patients for this study were those with National Comprehensive Cancer Network (NCCN) intermediate- or high-risk prostate adenocarcinoma; metastatic patients and those treated previously with prostatectomy or radiation therapy were excluded. The Michigan Urological Surgery Improvement Collaborative, another prospectively collected statewide quality improvement consortium, was accessed for additional baseline data as patients are linked within the 2 databases.

We limited our analysis to patients who started EBRT after the FLAME trial was presented at the ASTRO 2020 Annual Meeting (October 26, 2020).[8] Patients receiving brachytherapy were excluded from microboost analyses. Dosimetric analysis included patients who received conventional, hypofractionated, and stereotactic treatment courses defined as permissible on ongoing NRG trials for an intermediate and high-risk disease that allow for microboost (NRG GU-010 [NCT05050084] and NRG GU-009 [NCT04513717], respectively; Table E1). Intent of microboost was documented in prospectively completed forms at the time of treatment. In addition, MROQC prospectively collects all DICOM files for prostate cancer patients treated within the consortium, and dose-volume histogram (DVH) data were obtained and reviewed via MIM software. This study was institutional review board exempt as part of a quality improvement initiative. MROQC is financially supported by Blue Cross Blue Shield of Michigan (BCBSM) and the Blue Care Network of Michigan as part of the BCBSM Value Partnerships Program.

Statistical analysis

The primary outcome was the receipt of an EBRT microboost. Univariable and multivariable analyses were

performed to test the associations between patient, tumor, and treatment-related factors and microboost receipt. A logistic regression analysis was performed in the entire patient population to identify covariates (T stage, grade group, prostate-specific antigen, and RT planning/procedures) associated with the receipt of a microboost. We also used a mixed model with a random intercept for the treating center to assess for variability in microboost use that may be due to facility-level factors. For a sensitivity analysis, the analyses were repeated for the subset of patients treated by facilities that used microboost at least once. MIM software was used for DVH analyses as well as for equivalent dose in 2 Gy (EQD2) calculations, using an alpha/beta (α/β) ratio of 1.5 for prostate cancer and 2.5 for bladder and rectum. DVH curves with median and interquartile EQD2 doses were plotted for bladder, rectum, and prostate targets. Dosimetric parameters for patients treated with and without a microboost were compared, and the percent exceeding current NRG GU-009 and NRG GU-010 protocol conventional fractionation (1.8-2.0 Gy/fraction) constraints were calculated. All analyses were performed in SAS (version 9.4).

Results

Patient and treatment characteristics

A total of 741 patients were treated across 26 sites within MROQC from October, 26, 2020, to June, 26, 2023. Primary EBRT was used in 524 patients (71% of the entire cohort, Table 1), whereas combination brachytherapy was performed in 217 patients across 9 of 26 sites (Table E2). Of patients receiving EBRT alone, the median age was 71 years, and approximately 70% had NCCN intermediate-risk disease and 30% had high-risk disease. Most had clinical T1 disease (77%), and 53% had grade group 3-5 disease.

Of EBRT patients, 10% (n = 53/524) received an EBRT microboost. Seven sites treated at least one patient with an EBRT microboost, and these centers accounted for >60% of the total population receiving EBRT; the proportion treated with a microboost at each center is illustrated in Fig. 1. The cohorts did not significantly differ by pretreatment prostate-specific antigen, grade group, T stage, and NCCN risk stratifications, but they did differ by race and practice setting (Table 1). The rate of microboost use during the study period did not significantly change over time (10.0% in 2020, 9.1% in 2021, 10.7% in 2022, and 10.9% in 2023, 2-sided P value of .62 for trend). No trend was observed on a sensitivity analysis excluding the highest contributing center.

Several fractionation schemes were used across the consortium. Patients most commonly received moderate hypofractionation (20-28 fractions, n = 342/524), regardless of whether a microboost was prescribed (Table 2), whereas approximately 20% (n = 120/524) in each cohort received ultrahypofractionation (≤5 fractions). The most used moderate hypofractionation schedule was 70 Gy in 28 fractions (71%), followed by 62 Gy in 20 fractions (13%). Androgen deprivation therapy (ADT) was recommended for 56% of EBRT patients (n = 296/524); the intended duration was ≥6 to <18 months in 45% and ≥18 months in 33%. There were no significant differences between the 2 cohorts in terms of ADT recommendation (P = .24), intended ADT duration (P = .22), and fractionation (P = .09).

Table 2 describes differences in radiation planning and delivery between cohorts. Among patients receiving EBRT, univariable analysis revealed that those prescribed a microboost were more often planned with both computed tomography and MRI imaging (94% vs 65%, P < .0001). The microboost cohort was also more likely to undergo placement of both fiducial markers and rectal spacer (75% vs 44%, P < .0001). Rates of planning MRI and fiducial marker with rectal spacer placement stratified by the center are illustrated in Fig. E1. Median and mean expansion margins added to the prostate (± seminal vesicles) clinical target volume to define the planning target volume (PTV) were significantly smaller in the "Microboost" cohort when expanded nonuniformly in the anterior, superior, and right/left directions (Table 2; Table E3). However, of plans with uniform expansion margins, the "no microboost" cohort had a smaller mean (0.4 cm vs 0.5 cm) compared with the microboost cohort, although a wider range (0-0.8 cm vs 0.3-0.5 cm). The prostate PTV was significantly smaller in the microboost cohort (91 vs 127 cc, P < .0001). The contoured bladder and rectum volumes were not significantly different between the cohorts. Of patients receiving a microboost, the median intraprostatic boost gross tumor volume (GTV) was 20.7 cc (interquartile range: 11.4-34.4).

Multivariate analysis of microboost receipt

In a logistic regression model of the entire EBRT cohort, factors significantly associated with microboost receipt were grade group 4/5 disease (odds ratio [OR] = 2.55; 95% confidence interval [CI]: 1.13-5.62, P = .02), use of MRI for treatment planning (OR = 6.34; 95% CI: 2.16-27.12, P < .01), and placement of both fiducial markers and rectal spacer (ie, advanced image-guided radiation; OR = 2.94; 95% CI: 1.31-7.57, P = .01, Fig. 2). On a mixed model using a random intercept for the center, there was significant facility-level variation (P < .0001) beyond that attributable to clinical factors. In this model, only grade group 4/5 disease remained significantly associated with microboost use (OR = 3.88; 95% CI: 1.68-8.95, P < .01), whereas MRI planning and advanced image-guided radiation techniques were no longer significantly associated with receipt of microboost.

Table 1 Patient and treatment characteristics of each cohort

	EBRT w/o microboost (n = 471)*	EBRT w/ microboost (n = 53)*	*P* value†
Age, y, median	71	71	.88
Race			<.0001
White	404 (85.8%)	34 (64.2%)	
Black or African American	52 (11.0%)	19 (35.8%)	
Other	15 (3.2%)	0 (0%)	
Charlson comorbidity score			.13
0	298 (63.3%)	26 (49.1%)	
1	93 (19.7%)	14 (26.4%)	
2+	80 (17.0%)	13 (24.5%)	
Academic practice setting	108 (22.9%)	5 (9.4%)	.02
Pretreatment PSA, median (ng/mL)	8.4	7.1	.47
Pretreatment PSA			.11
0-<10 ng/mL	287 (60.9%)	40 (75.5%)	
≥10-<20 ng/mL	132 (28.0%)	10 (18.9%)	
≥20 ng/mL	52 (11.0%)	3 (5.7%)	
Grade group			.75
1/2	224 (47.6%)	23 (43.4%)	
3	151 (32.1%)	17 (32.1%)	
4/5	96 (20.4%)	13 (24.5%)	
Clinical T stage			.21
T1	355 (75.4%)	47 (88.7%)	
T2	93 (19.7%)	5 (9.4%)	
T3	10 (2.1%)	1 (1.9%)	
T4	0 (0%)	0 (0%)	
TX	7 (1.5%)	0 (0%)	
NCCN risk group			.17
Favorable intermediate	99 (21.0%)	17 (32.1%)	
Unfavorable intermediate	232 (49.3%)	21 (39.6%)	
High	140 (29.7%)	15 (28.3%)	
EBRT fractionation			.09
Ultra-hypofractionation (≤5)	110 (23.4%)	10 (18.9%)	
Moderate hypofractionation (20-28)	310 (65.8%)	32 (60.4%)	
Conventional fractionation (>28)	50 (10.6%)	11 (20.8%)	
ADT recommended			.24
Yes	270 (57.3%)	26 (49.1%)	
No	175 (37.2%)	21 (39.6%)	
Patient Refused	16 (3.4%)	4 (7.5%)	
Total ADT duration intended			.22
>0-<6 mo	17 (6.3%)	3 (11.5%)	
≥6 mo to <18 mo	117 (43.3%)	17 (65.4%)	
≥18 mo	91 (33.7%)	6 (23.1%)	

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen.

*n (%) or median; may not sum to 100% due to missingness.

†*t*-test for continuous variables, chi-squared for categorical variables.

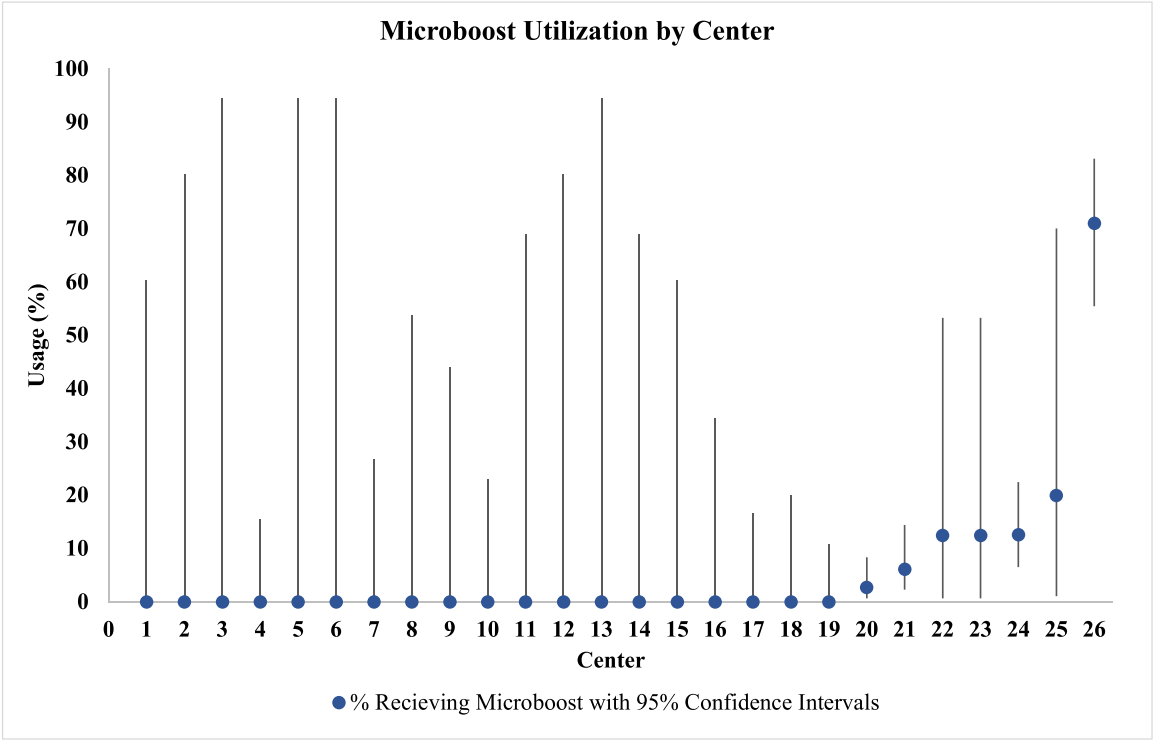

Figure 1 Percent of patients receiving microboost by the state consortium center.

Sensitivity analysis limited to only centers treating at least one patient with a microboost was similar to the primary analysis, with both models identifying grade group 4/5 disease being significantly associated with microboost receipt (Table E4).

Dosimetric analysis

Of patients treated with EBRT, 463 (88%) DVHs were available and eligible for dosimetric analysis. Reasons for ineligibility were unavailable DICOM files (n = 23) and nonstandard fractionation schedules per ongoing NRG GU-009 and GU-010 trials (n = 38). After EQD2 conversions, DVH curves for the bladder, rectum, and prostate (± seminal vesicles) PTV for the cohorts were plotted at 0.1 EQD2Gy increments, with the median and interquartile ranges illustrated in Fig. 3. Dosimetric parameters for targets are shown in Table 3. The median D95% (% of prescription dose) for the prostate PTV was 100% for both cohorts. The median intraprostatic GTV D98% (EQD2Gy) was 94.4 Gy for microboost patients, and 92.5% had a D98% (EQD2Gy) greater than 85 Gy. The median mean GTV dose was 98.9 EQD2Gy.

The percent receiving a dose greater than 94 EQD2Gy (ie, above the median GTV D98%) to at least 20 ccs of PTV (ie, the median GTV volume) was 24.5% in the "no microboost" cohort and 56.8% for the microboost cohort ($P < .0001$). When excluding patients receiving ultrahypofractionation (≤5 fractions), the difference was 0% vs 47% ($P < .0001$). The maximum allowable boost dose on the FLAME trial was 113.4 EQD2Gy ($\alpha/\beta = 1.5$), and only 10% of non-SBRT microboost patients exceeded a maximum PTV dose >114 EQD2Gy (Table 3).

Median volumetric parameters for both rectum and bladder were calculated, and these were compared with the current conventional fractionation perprotocol constraints from NRG GU-009 and GU-010 (Table E5). The median volumes receiving all assessed doses (ie, V80 Gy, V75 Gy, etc) were below all NRG constraints. For most NRG rectal constraint dose levels (V65, V70, V75, and V80), microboost patients had statistically significantly smaller volumes receiving each dose, but volumes for bladder constraint doses did not differ between cohorts. Furthermore, the percent of patients exceeding each NRG rectal and bladder constraint was very low and did not significantly differ between the 2 cohorts. For rectal constraints, the V80Gy ≤ 5% was exceeded in 8% of the "No Microboost" cohort and 5.4% of the "Microboost" cohort ($P = .57$), whereas no patient in either cohort exceeded the V70Gy, V65Gy, and V50Gy constraints. For bladder constraints, approximately 25% of each cohort exceeded the V80Gy ≤ 10%, but only ≤2% exceeded the V70Gy, V65Gy, and V50Gy constraints. Blended DVH curves for the bladder and rectum suggested that these organs at risk (OARs) were receiving higher intermediate doses in the microboost cohort (Fig. 3A, C). To investigate, volumes receiving a range of EQD2 doses in 5 Gy increments were compared between cohorts

Table 2 EBRT planning and delivery techniques

	EBRT w/o microboost (n = 471)*	EBRT w/ microboost (n = 53)*	*P* value†
EBRT target delineation			<.0001
CT simulation and MRI	306 (65.0%)	50 (94.4%)	
CT only	165 (35.0%)	3 (5.7%)	
Procedures prior to simulation			<.0001
Fiducial markers + rectal spacer	211 (44.8%)	40 (75.5%)	
Fiducial markers only	44 (9.3%)	6 (11.3%)	
Rectal spacer only	30 (6.4%)	0 (0%)	
Neither	186 (39.5%)	7 (13.2%)	
Prostate CTV to PTV expansion margins (cm)			
Uniform margin, N	182 (38.5%)	37 (69.8%)	
Expansion margin	0.5 (0.3, 0.5)	0.5 (0.5, 0.5)	.002
Nonuniform margins, N	229 (48.6%)	11 (20.8%)	
Anterior	0.5 (0.5, 0.7)	0.5 (0.4, 0.6)	.03
Posterior	0.4 (0.4, 0.5)	0.3 (0.3, 0.5)	.43
Superior	0.6 (0.5, 0.7)	0.5 (0.5, 0.6)	.09
Inferior	0.6 (0.5, 0.7)	0.5 (0.5, 0.6)	.10
Right	0.5 (0.5, 0.7)	0.5 (0.4, 0.6)	.03
Left	0.5 (0.5, 0.7)	0.5 (0.4, 0.6)	.03
Contour volumes (cc)			
Prostate PTV	127.4 (92.2-170.7)	91.4 (68.9-111.0)	<.0001
Intraprostatic GTV	—	20.7 (11.4-34.4)	—
Bladder	219.6 (142.3-352.6)	187.2 (118.4-337.8)	.0583
Rectum	73.1 (56.8-88.9)	69.9 (60.1-95.2)	.5336

Abbreviations: CT = computed tomography; CTV = clinical target volume; EBRT = external beam radiation therapy; GTV = gross tumor volume (of intraprostatic disease); MRI = magnetic resonance imaging; PTV = planning target volume (of prostate [± seminal vesicles]).
*n (%) or median (interquartile range); may not sum to 100% due to missingness.
†*t*-test for continuous variables, chi-squared for categorical variables.

(Table E5). For the rectum, several parameters were significantly higher in microboost patients, particularly the V20Gy (53.8% vs 36.5%, $P = .03$) and V25Gy (42.3% vs 28.9%, $P = .04$). The differences for bladder parameters were less pronounced and nonsignificant.

Discussion

Our study demonstrates that across a diverse, statewide radiation oncology quality consortium, the use of microboost for radiation dose escalation in localized prostate cancer is infrequent. Only approximately 10% of patients treated with EBRT received microboost. Although grade group 4/5 tumors were associated with increased microboost usage, there remains significant facility-level heterogeneity. On dosimetric analysis, we found excellent target coverage, with the majority of plans meeting current NRG protocol constraints for bladder and rectum.

Several recent trials have evaluated the safety and efficacy of an EBRT microboost for intraprostatic gross disease. The FLAME trial was the first prospective phase 3 trial to demonstrate improved biochemical disease-free survival with an EBRT microboost without increasing late gastrointestinal/genitourinary toxicities.[8] Analysis suggested that biochemical failure is inversely correlated with achieved dose to gross disease,[8] and a secondary analysis reported improvements in both local failure and combined regional/distant metastatic failure.[14] Similarly, the DELINEATE trial reported favorable toxicity profiles and 5-year biochemical control with microboost via both conventionally and moderately hypofractionated courses.[9] The phase 2 Hypo-FLAME trial found acceptable acute GU/GI toxicity with the delivery of ultrahypofractionated microboost, comparable with other standard ultrahypofractionated trials.[15] The ongoing PIVOTALboost trial

	Logistic Regression Model		Mixed Model with Random Intercept	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Grade Group				
Grade Group 3 vs. 1/2	1.49 (0.74 – 2.97)	0.26	1.77 (0.56 – 5.60)	0.33
Grade Group 4/5 vs. 1/2	2.55 (1.13 – 5.62)	0.02	3.88 (1.68 – 8.95)	<0.01
T Stage				
T3/T4 vs. T1/T2	0.58 (0.03 – 3.47)	0.62	0.84 (0.15 – 4.61)	0.84
PSA				
PSA 10-19 vs. PSA <10 ng/mL	0.51 (0.23 - 1.05)	0.08	0.72 (0.27 – 1.95)	0.52
PSA ≥20 vs. <10 ng/mL	0.45 (0.10 – 1.38)	0.21	0.63 (0.26 – 1.51)	0.30
Planning/Procedures				
CT + MRI vs. CT Only	6.34 (2.16 – 27.12)	<0.01	2.07 (0.24 – 18.01)	0.51
Fiducial Markers + Rectal Spacer (Yes vs. No)[1]	2.94 (1.31 – 7.57)	0.01	2.29 (0.81 – 6.45)	0.12

[1] "No" = fiducial markers only, spacer only, or neither

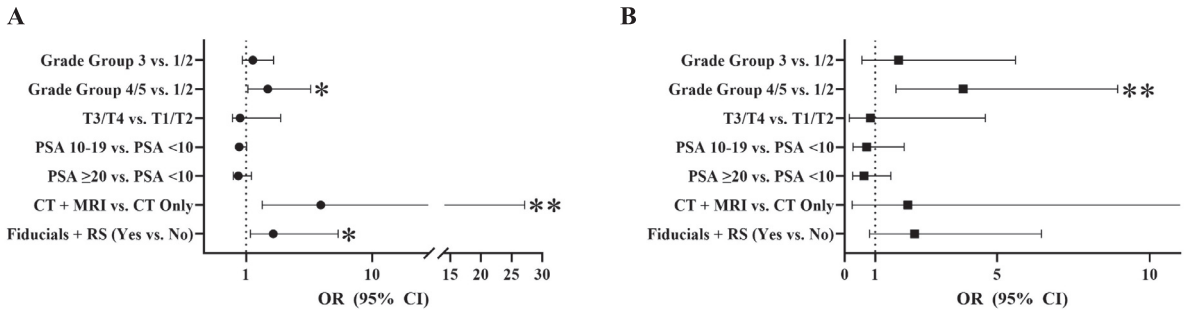

Figure 2 Forest plots of logistic regression model (A) and mixed model with random intercept for facility (B).
Abbreviations: PSA = prostate-specific antigen; RS = rectal spacer.

(CRUK/16/018, ISRCTN80146950) is a multiarm trial comparing prostate-only radiation against the addition of either pelvic nodal irradiation and/or a focal boost (via EBRT or high dose rate brachytherapy) in men with localized prostate cancer with adverse features.[17] As positron emission tomography (PET) imaging becomes more frequent in the localized setting, the phase 2 ARO2020-01 trial importantly confirmed the feasibility and safety of focal boost to lesions defined on both prostate-specific membrane antigen (PSMA)-PET and MRI.[18] A phase 3 trial using this approach to deliver an ultrahypofractionated microboost is underway (NCT06330909).[19] These trials will be crucial to confirming the benefit of microboost and increasing the evidence to promote adoption in routine practice.[17]

In our primary logistic regression analysis, grade group 4/5 disease, use of MRI planning, and fiducial marker and rectal spacer use were all associated with microboost receipt. When using a random intercept to assess for facility-level heterogeneity, grade group 4/5 was significantly associated with microboost, whereas MRI planning and fiducial/spacer usage were not. One possible explanation for this observation is that facilities using these advanced techniques are also more likely to utilize a microboost, but within a given facility, the use of these techniques does not directly impact a provider's decision to prescribe a microboost or not. Within these treating facilities, physicians appear to be selecting patients with more aggressive pathology to receive microboost, perhaps believing these patients could derive the most benefit from dose escalation. This is supported by a post-hoc analysis FLAME trial, which found that those with high-risk features, particularly grade group 4/5 disease, obtained the most benefit from a microboost.[20] The aforementioned ongoing PIVOTALboost trial is enrolling NCCN intermediate-risk patients with adverse features or high-risk patients and may help define subgroups that benefit most from focal boost.[17] The low and heterogeneous uptake in real-world clinical practice captured by this study is in contrast to recently published social media survey data suggesting that 45% of Radiation Oncologists in high-income countries "routinely" use microboost.[16] Our data represent all patients treated within a large diverse statewide consortium, with robust prospective collection of treatment and patient data, and may more accurately portray microboost utilization.

Our dosimetric analysis suggests that microboost prescriptions within MROQC are both within a range expected to convey clinical benefit and are being delivered with reasonable doses to OARs. The median mean EQD2 dose to the intraprostatic GTV (98.9 Gy) is comparable with that reported in the FLAME trial (106.3 Gy EQD2, $\alpha/\beta = 1.5$).[8] Furthermore, >90% of microboost patients in MROQC had a D98% ≥85 Gy EQD2, which has been associated with low local and regional/distant failure on a secondary analysis of the FLAME trial.[14] A necessary component to minimizing added toxicity with an EBRT microboost is optimal treatment planning and delivery. The FLAME, DELINEATE, and hypo-FLAME trials defined their GTV on multiparametric MRI, and all trials used gold fiducial markers for treatment positioning and verification with protocol-mandated constraints on OARs (eg, bladder and rectum).[8,9,15] Encouragingly, in patients receiving a microboost within MROQC, we found very high rates of both MRI use for radiation planning and

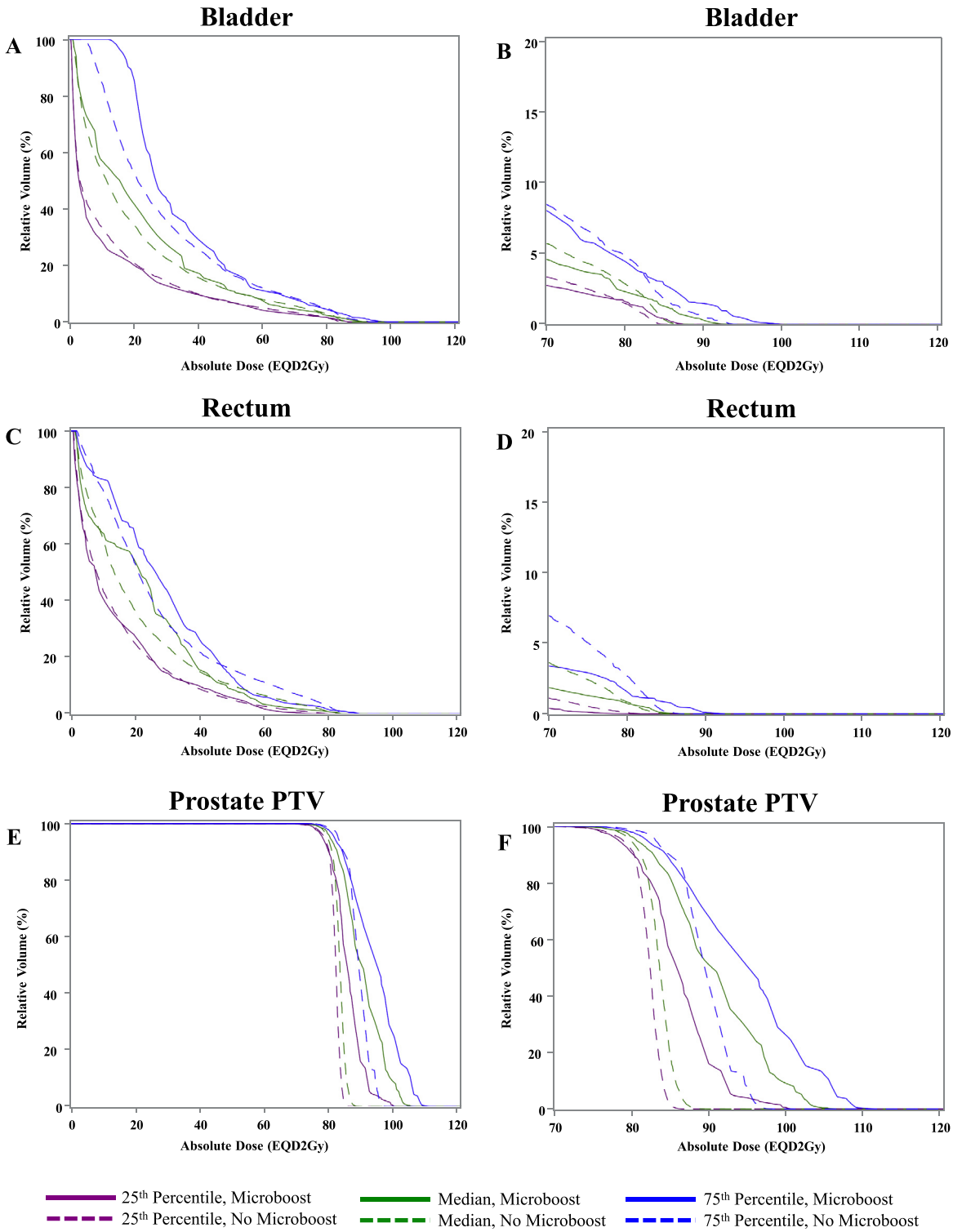

Figure 3 Median and interquartile dose-volume histogram curves for no microboost cohort (dashed line) and microboost cohort (solid line) for bladder (A), rectum (C), and PTV (E), with a focus on each for the EQD2 dose ≥70 Gy in panels (B), (D), and (F), respectively.

placement of fiducial markers combined with rectal spacers. Rectal spacers were only used in some patients on recent SBRT microboost trials and were not used in patients treated on FLAME/DELINEATE.[8-10,15] Whether rectal spacers are necessary to maintain isotoxicity with hypofractionated regimens is unclear; however, the current high use inMROQC may reflect a belief that these can facilitate safe microboost delivery.

Table 3 Dosimetric parameters for prostate (± seminal vesicles) PTV and intraprostatic boost GTV

Parameter	EBRT w/o microboost*	EBRT w/ microboost*	*P* value†
Intraprostatic GTV			
D98% (EQD2), median	—	94.4 Gy	—
Mean dose (EQD2), median	—	98.9 Gy	—
Prostate PTV, entire cohort			
Median D95% (% of prescription)	100%	100%	.08
Median V74EQD2Gy (%)	99.9%	99.9%	.99
% w/ max dose >114 Gy (EQD2)	21.40%	27%	.43
% w/ 20 cc of PTV >94 Gy (EQD2)	24.5%	56.8%	<.0001
% w/ 30 cc of PTV >94 Gy (EQD2)	23.8%	43.2%	.009
Prostate PTV, excluding SBRT			
% w/ max dose >114 Gy (EQD2)	1%	10%	.0003
% w/ 20 cc of PTV >94 Gy (EQD2)	0.0%	47%	<.0001
% w/ 30 cc of PTV >94 Gy (EQD2)	0.0%	30%	<.0001

Abbreviations: GTV = gross tumor volume (of intraprostatic disease); PTV = planning target volume (of prostate [± seminal vesicles]).
*Median (Gy or %) or % of patients.
†*t*-test for continuous variables, chi-squared for categorical variables.

A unique strength of our study was the ability to analyze patient-level DICOM data for patients treated by a variety of physicians across different centers. Plans exceeding current NRG trial protocol constraints for bladder and rectum were low and did not differ between cohorts, suggesting that high-quality radiation planning is present across MROQC, and that stricter constraints could feasibly be implemented across the consortium and potentially in future NRG trials. Despite the observational nature of MROQC and important cohort imbalances (eg, PTV size, use of fiducials/rectal spacer), these results suggest the selective real-world implementation of microboost may be isotoxic. However, in microboost patients, the volume of bladder/rectum receiving intermediate doses was higher across a spectrum of tested dose levels. These levels are below current NRG constraints, and prospective evaluation of the clinical significance of these intermediate cutpoints is limited. A secondary analysis of the TROG 03.04 RADAR trial DVH data reported significant associations between different GI toxicities and low and mid-range dose-volume thresholds to different anatomic GI substructures.[21] This included doses to the anorectum ranging from 12 to 36 Gy (EQD2, α/β = 3.0) being associated with urgency, tenesmus, and diarrhea, and doses <40 Gy (EQD2, α/β = 3.0) to the anal canal is associated with increased stool frequency, incomplete evacuation, and bleeding.[21] A secondary analysis of RTOG 0126 found no differences in bladder/rectum V40Gy, V50Gy, and V60Gy volumes between the 70.2 Gy and 79.2 Gy arms, with no correlation between higher doses these OARs and worse patient-reported outcomes.[22] A dosimetric analysis of the POP-RT trial found intermediate bladder doses (V10 and V40) were not associated with worse grade 2+ urinary toxicity.[23] Independent validation of intermediate-dose thresholds, and the importance of GI substructures, is warranted and should be considered in future focal dose escalation trials, given the results presented herein.

Some limitations to our analysis exist. Given the nonrandomized use of microboost within MROQC, there are likely imbalances not accounted for between the examined groups that could influence microboost prescription. Clinical target volume was not available in our data set, limiting our ability to determine whether the difference in PTV volumes was due to expansion margins or if providers were selecting patients with smaller prostate sizes for boosting. Furthermore, there was no standardized approach to defining microboost targets, OARs, nor standardized radiation planning constraints between centers. MROQC is also unable to capture a decision to boost intraprostatic disease without a specific GTV volume contoured and boost prescription, for example, informally directing a dosimetrist to center hotspots in an area of the known gross tumor. Our analysis may therefore underestimate the true rate of microboost intent. However, the rate of patients within the no microboost cohort receiving the median microboost cohort's GTV D98% (Gy) to ≥ 20 ccs of PTV was very small and only occurred in SBRT patients, suggesting we captured the majority of intended microboost cases. We were also unable to evaluate whether all patients would meet contemporary definitions of suitability for microboost. The majority of our population would have met the broad inclusion criteria of the FLAME trial,[24] but the ongoing PIVOTALboost trial is

limiting inclusion to those with PI-RADS 4 to 5 lesions >5 mm with lesion volume <50% of the total prostate volume.[17] Given that only 7 of 26 centers within MROQC are using a microboost, our findings likely truly reflect both underutilization and facility variability. National guidelines first endorsed the use of a conventionally fractionated microboost in 2023, and how this influences provider decisions with statewide consortium was beyond the scope of this study. Our dosimetric analysis is inherently constrained by assumptions made for EQD2 conversions, although fractionation schedules did not different between cohorts. The alpha/beta (α/β) ratio used for prostate (1.5) is supported by NRG protocols (GU-009 and GU-010), and the α/β of 2.5 for bladder/rectum is based on toxicity analyses from the CHHiP trial.[25,26] Although our results suggest higher intermediate doses to OAR in microboost patients, whether these differences are causally related and translate to meaningful clinical differences in toxicity is unclear, and validation with prospective, randomized data is necessary. MROQC is collecting patient-reported outcomes and survival endpoints prospectively, and detailed analyses correlating these with microboost use may be possible in the future.

Conclusions

EBRT microboost to a dominant intraprostatic lesion is an emerging dose escalation strategy for localized prostate cancer supported by several prospective trials, but our analyses suggest that it is infrequently used in routine clinical practice. Heterogeneity in use may be influenced by adverse pathology and appears facility-dependent. Selective real-world use of microboost may not increase the proportion of radiation plans exceeding NRG constraints, but attention to normal tissue dose is critical to ensure safety when a microboost is used. Future work is needed to address barriers to microboost utilization, which may include increasing access to MRI, improving physician and dosimetrist education, building on current evidence with high-quality randomized trials (ie, PIVOTALboost), and identifying patient subgroups that derive the most clinical benefit.

Disclosures

Robert Dess reports financial support was provided by Blue Cross Blue Shield of Michigan and serves in a consulting or advisory role for Janssen Biotech. Matthew Schipper reports financial support was provided by Blue Cross Blue Shield of Michigan and receives consulting fees from Innovative Analytics. Melissa Mietzel reports financial support was provided by Blue Cross Blue Shield of Michigan. Margaret Grubb reports financial support was provided by Blue Cross Blue Shield of Michigan. Danielle Kendrick reports financial support was provided by Blue Cross Blue Shield of Michigan. Huiying Yin reports financial support was provided by Blue Cross Blue Shield of Michigan. Dale Litzenberg reports financial support was provided by Blue Cross Blue Shield of Michigan. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. William Jackson receives research funding from Janssen. All remaining authors have no conflicts of interest to disclose.

Acknowledgments

We would like to thank Michigan Radiation Oncology Quality Consortium is financially supported by Blue Cross Blue Shield of Michigan (BCBSM) and the Blue Care Network of Michigan as part of the BCBSM Value Partnerships Program. Matthew Schipper performed the statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101629.

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