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Incorporation of Biologic Response Variance Modeling Into the Clinic: Limiting Risk of Brachial Plexopathy and Other Late Effects of Breast Cancer Proton Beam Therapy

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Abstract

Purpose: The relative biologic effectiveness (RBE) rises with increasing linear energy transfer toward the end of proton tracks. Presently, there is no consensus on how RBE heterogeneity should be accounted for in breast cancer proton therapy treatment planning. Our purpose was to determine the dosimetric consequences of incorporating a brachial plexus (BP) biologic dose constraint and to describe other clinical implications of biologic planning.

Methods and Materials: We instituted a biologic dose constraint for the BP in the context of MC1631, a randomized trial of conventional versus hypofractionated postmastectomy intensity modulated proton therapy (IMPT). IMPT plans of 13 patients treated before the implementation of the biologic dose constraint (cohort A) were compared with IMPT plans of 38 patients treated on MC1631 after its implementation (cohort B) using (1) a commercially available Eclipse treatment planning system (RBE = 1.1); (2) an in-house graphic processor unit-based Monte Carlo physical dose simulation (RBE = 1.1); and (3) an in-house Monte Carlo biologic dose (MCBD) simulation that assumes a linear relationship between RBE and dose-averaged linear energy transfer (product of RBE and physical dose = biologic dose).

Results: Before implementation of a BP biologic dose constraint, the Eclipse mean BP D0.01 cm³ was 107%, and the MCBD estimate was 128% (ie, 64 Gy [RBE = biologic dose] in 25 fractions for a 50-Gy [RBE = 1.1] prescription), compared with 100.0% and 116.0%, respectively, after the implementation of the constraint. Implementation of the BP biologic dose constraint did not significantly affect clinical target volume coverage. MCBD plans predicted greater internal mammary node coverage and higher heart dose than Eclipse plans.

Conclusions: Institution of a BP biologic dose constraint may reduce brachial plexopathy risk without compromising target coverage. MCBD plan evaluation provides valuable information to

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Supplementary Data

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physicians that may assist in making clinical judgments regarding relative priority of target coverage versus normal tissue sparing.

Introduction

Proton beam therapy (PBT) is increasingly being employed for the treatment of early-stage and locally advanced breast cancer.¹⁻⁴ Compared with photon therapy, PBT is attractive because of physical properties that enable sharp dose falloff beyond the target, resulting in a reduction in dose to nontarget normal tissue while maintaining or improving target volume coverage.⁵ Based on analyses from patients treated with photons correlating radiation therapy—related toxicity with dose to organs at risk, the hypothesis has been put forward that reducing exposure to the heart, lungs, muscles, bone, skin, and uninvolved normal breast tissue with PBT will decrease the risks of adverse events after breast cancer radiation therapy.⁶⁻⁹ Furthermore, it has been suggested that more robust target coverage of anatomically challenging areas like the internal mammary node (IMN) basin with PBT could reduce rates of relapse and death from breast cancer in some high-risk patients.^{5,10,11}

However, PBT does add unique complexities to the treatment planning process that are distinct from photon therapy. For example, PBT is more sensitive to soft tissue anatomic changes and some interfraction and intrafraction setup uncertainties that must be accounted for during PBT treatment planning and delivery.^{12,13} Variability in proton relative biologic effectiveness (RBE) is increasingly recognized as an additional uncertainty that could affect clinical outcomes.¹⁴

RBE can be defined as the ratio of doses of 2 radiation modalities that cause the same biologic effect. A proton RBE of 1.1 has been used in the clinic based on a meta-analysis of in vitro and in vivo data on the biologic impact of protons delivered at the middle of the spread-out Bragg peak.¹⁵ However, numerous studies have now shown that the RBE is greater than 1.1 at the Bragg peak, and distal falloff where the radiation ionization density (ie, the linear energy transfer [LET]) quickly rises as each particle comes to a stop.¹⁶⁻¹⁸ Pencil beam scanning—based intensity modulated proton therapy (IMPT) is a particularly attractive proton therapy technique for breast cancer due to its ability to constrain the dose to the skin surface and deliver a more conformal treatment. However, in contrast to passively scattered proton therapy, where regions of increased LET are highly predictable, with IMPT, areas of high LET could fall almost anywhere in the target volume.¹⁹ Such heterogeneity in LET and RBE raises the concern that despite the reduced dose to normal tissues with PBT, “biologic hot spots” of PBT may actually paradoxically increase the risk of some adverse effects if not mitigated during treatment planning.²⁰ Presently, there is no consensus on how RBE variability should be accounted for in breast cancer treatment planning.

Brachial plexopathy is a rare but potentially debilitating late adverse effect of breast cancer nodal irradiation. Clinically, patients with brachial plexopathy may present with paresthesias or pain, which can even progress to loss of arm motor function.²¹ The risk of brachial plexopathy has been correlated with increased dose to the brachial plexus (BP) and larger fraction size.²² Women with breast cancer undergoing regional nodal irradiation may have excellent prognoses and years to develop late complications of therapy.²³ With this

background in mind, we investigated the feasibility of implementing physical and biologic dose constraints for the BP in the context of MC1631, a randomized trial of 15- versus 25-fraction IMPT after mastectomy in patients with breast cancer requiring regional nodal irradiation (NCT02783690). The goal of the BP constraint was to mitigate the risk of late brachial plexopathy with either conventional or hypofractionated PBT. The purpose of this manuscript is to report the dosimetric consequences of incorporating a brachial plexus constraint. In addition, we present data on biologic and physical dose relating to target coverage and organ-at-risk exposure to demonstrate how other information provided by biologic dose simulation can be used in the clinic as part of routine breast cancer treatment planning.

Methods and Materials

Patients

This study was approved the Mayo Clinic institutional review board (IRB). After institutional review board approval, we selected 2 cohorts of patients who were treated with postmastectomy IMPT for breast cancer at our institution between July 2015 and May 2017. Cohort A consisted of 13 consecutive patients treated with postmastectomy IMPT as part of a prospective registry (NCT02457962) between July 2015 and March 2016, before the implementation of a BP physical and biologic dose constraint in our clinic. Cohort B consisted of 38 consecutive patients treated with postmastectomy IMPT between June 2016 and May 2017 after the implementation of a BP physical and biologic dose constraint enrolled on MC1631, an ongoing randomized trial of 15 versus 25 fractions pencil beam scanning proton radiation therapy after mastectomy in patients requiring regional nodal irradiation (NCT02783690).

Treatment planning

The details of our immobilization, computed tomography (CT) simulation, and IMPT treatment planning process have previously been described.¹ In brief, patients were most commonly immobilized supine on a breast board with arms up and in a thermoplastic facemask to reproducibly maintain head and neck position. CT simulation was done with 2-mm slices at 120 kVp, routinely in free breathing. The clinical target volume (CTV) included the chest wall and regional lymph nodes (axilla, supraclavicular, and IMN basins) and was delineated and reported as a single structure. The CTV resembled the Radiation Therapy Oncology Group Breast Cancer Atlas with some notable exceptions based on previously published nodal mapping studies. First, the chest wall CTV routinely extended no deeper than the anterior surface of the ribs and intercostal muscles except in the vicinity of the IMNs.²⁴ The CTV was extended to include the ribs and intercostal muscles if these structures were invaded. Second, both the medial and lateral supraclavicular lymph nodes were routinely included. However, the supraclavicular CTV was not routinely extended medial to the lateral border of the internal carotid artery to reduce the dose to midline organs given the low risk of nodal presentation or recurrence immediately adjacent to the esophagus and trachea.^{25,26} Finally, the IMN target volume was defined as a 4- to 5-mm medial and lateral expansion on the internal mammary vessels and extended from the cranial CT slice of the fourth rib to the most caudal extent of the supraclavicular volume near the junction of the

internal mammary and brachiocephalic veins. In addition to being encompassed in the chest wall and regional nodal CTV, dosimetry was also evaluated and reported separately for the IMN target volume.²⁷

Patients were treated with a median of 2 multifield optimized anterior-oblique beams arranged at approximately 45°. The prescription dose was either 50 Gy (RBE 1.1 in 25 fractions or 40 Gy (RBE 1.1) in 15 fractions. Focal lymph node boosts, but not chest wall boosts, were permitted. Plans were constructed in the Eclipse (Varian Medical Systems, Palo Alto, CA) planning system. For treatment planning, setup uncertainty analyses simulating worst-case scenarios of ± 5 mm shifts in isocenter along each translation axis and $\pm 3\%$ beam range uncertainty were performed for the CTV and organs at risk. Target and normal tissue dose-volume objectives have previously been reported.^{1,28} The first planning priority for both cohort A and cohort B was for 90% of the CTV (D90%) to receive 90% of the prescription dose under even the worst-case uncertainty analysis. The BP was contoured according to the validated and standardized method of Hall et al.²⁹ For the BP, the Eclipse plan physical dose constraint for cohort B only was maximum dose received by at least 0.01 cm³ of the volume (D0.01 cm³ 102% (RBE = 1.1).

Monte Carlo—based biologic dose calculation

All Eclipse breast cancer plans are checked by a very fast and accurate in-house graphic processor unit (GPU)-based Monte Carlo system, which our group previously described.³⁰ Like the dose calculated by the Eclipse treatment planning system, which is referred to in this article as the Eclipse physical dose (EPD [RBE 1.1]), our GPU-based Monte Carlo physical dose (MCPD [RBE 1.1]) model includes an RBE factor of 1.1. The MCPD (RBE 1.1) model has been extensively verified with the Tool for Particle Simulation software version beta-6 and Geant 4.9.6.³⁰ Furthermore, the GPU-based Monte Carlo handles nonelastic interactions on an event-by-event basis by employing a Bertini cascade simulation, enabling accurate dose-averaged LET computations.³⁰ To calculate Monte Carlo biologic dose (MCBD), a simple linear relationship between LET and biologic dose was assumed, as previously published by Beltran et al.³¹ According to the Beltran model, the MCBD approximates previously published models derived from fits to in vitro cell survival data.^{30,32–34} For the BP, the MCBD constraint for cohort B only was maximum dose received by at least 0.01 cm³ of the volume (D0.01 cm³ 120% (product of RBE and Monte Carlo physical dose = biologic dose). The MCBD dose was calculated after the Eclipse optimization (along with EPD [RBE 1.1] and MCPD [RBE 1.1]). If there were MCBD hotspots in the BP or other critical structures, the dosimetrist constrained these by a variety of techniques such as changing the beam angles, contouring certain areas, and constraining the physical dose within them or limiting the scanning regions for certain beams. After these changes were made, another round of Eclipse optimization was started, and the MCBD was recalculated and presented to the physician. This process can take several iterations before acceptable MCBD, EPD (RBE 1.1), and MCPD (RBE 1.1) distributions are obtained. In short, in this work the MCBD did not directly enter the optimization function; MCBD hotspots were mitigated in a “forward planning” (and not inverse planning) fashion.

Figure 1 displays BP dose-volume histograms and axial and coronal color wash images at the level of the BP for both the EPD (RBE 1.1) and the MCBD plans of a typical patient in cohort B with the BP physical and biologic dose constraints applied. The primary planning priority for the heart was to limit the mean heart dose to 1.5% of prescription, but attempts to limit hot spots (ie, prescription dose) were also made on the EPD (RBE 1.1) and the MCBD plans.

Outcomes

Categorical clinical variables were compared between the 2 cohorts using chi-squared tests or Fisher exact tests as appropriate. Target coverage and normal tissue dosimetric parameters for the CTV, IMNs, heart, lungs, ipsilateral breast, and skin were compared using the Wilcoxon rank-sum test. Provider assessment of early and late adverse events was performed using the Common Toxicity Criteria for Adverse Events version 4.0. Tenpoint linear analog scale assessment questions were used to assess patient-reported arm symptoms and are provided in the Appendix E1 (available online at <https://doi.org/10.1016/j.prro.2019.08.011>).³⁵ The primary emphasis of the patient-reported outcomes analysis was the difference between baseline and follow-up scores to account for any variability in baseline conditions. The 2-sided Welch-Satterthwaite t test was used to assess for differences in changes of patient-reported arm function between the 2 cohorts.

Results

The median follow-up for all patients was 24 months (range, 12-45 months). Clinical characteristics of the 13 patients treated before the implementation of a BP physical and biologic dose constraint (cohort A) and the 38 patients treated with postmastectomy IMPT after the implementation of a BP physical and biologic dose constraint (cohort B) are displayed in Table 1. Patients in cohort A were younger and more commonly presented with clinical stage 3 and left-sided disease. There were no differences in tumor grade, estrogen receptor, progesterone receptor, or human epidermal growth factor receptor 2 status.

BP doses, CTV coverage, and arm toxicity

As demonstrated in Figure 2 using $\alpha/\beta = 2$ Gy, the BP biologic dose as determined by the Beltran MCBD model used for our study was comparable to other previously published models by Carabe et al, McNamara et al, and Wedenberg et al derived from fits to in vitro cell survival data.³¹⁻³⁴ For cohort A and cohort B, the median BP D0.01 cm³ on the EPD (RBE 1.1), MCPD (RBE 1.1), and MCBD models were 107% versus 100% ($P < .0001$), 111% versus 103% ($P < .0001$), and 128% versus 116% ($P < .0001$), respectively (Table 2). According to our model, for a prescription of 50 Gy in 25 fractions, assuming an α/β ratio of 2 for late effects, the median BP MCBD D0.01 cm³ of 128% for cohort A translates into a biologically effective dose of 73 Gy in 2 Gy fractions. In contrast, the median BP MCBD D0.01 cm³ of 116% for cohort B translated into a more clinically acceptable biologically effective dose of 63 Gy in 2 Gy fractions.

To determine the impact of the BP constraints on target coverage, we also evaluated the CTV D95% before (cohort A) and after (cohort B) implementation of the BP constraints.

The median EPD (RBE 1.1), MCPD (RBE 1.1), and MCBBD CTV D95% were 99% versus 97% ($P = .0002$), 99% versus 97% ($P = .0404$), and 103% versus 101% ($P = .0854$) for cohort A and cohort B, respectively. Although the CTV D95% was significantly higher for cohort A in the EPD (RBE 1.1) and MCPD (RBE 1.1) plans, these absolute differences were small and likely of negligible clinical significance. Furthermore, we cannot rule out the possibility that other factors unrelated to the BP constraint could have affected differences in target coverage between the 2 cohorts, such as the more adverse disease biology in cohort A (Table 1).

There have been no brachial plexopathy adverse events to date. Patient-reported measures of arm function are being assessed prospectively, as displayed in Table 3. At 3 months compared with baseline, there were no significant differences between the 2 cohorts in the change in patient-reported ability to lift items over 10 pounds, to reach or extend the arm above shoulder level, or to bend and straighten the affected arm or in numbness or tingling of the ipsilateral arm.

IMN coverage and cardiac sparing

The steep dose gradients at the interface of the IMNs with the heart are areas of high LET in breast proton radiation therapy treatment plans resulting from optimizing for robust coverage of the IMN CTV while constraining cardiac dose. Therefore, we evaluated IMN CTV coverage and heart doses on the EPD (RBE 1.1) plans as well as the MCPD (RBE 1.1) and MCBBD models for all 51 patients (Table 4). There were no significant differences in IMN coverage or doses to organs at risk between the EPD (RBE 1.1) and MCPD (RBE 1.1) plans (all $P > .05$, not shown). Therefore, the primary emphasis of the analysis was the comparison between the MCPD (RBE 1.1) and MCBBD plans. As expected, owing to biologic range extension, the median IMN CTV D95% and heart Dmax were significantly greater for the MCBBD than for the MCPD (RBE 1.1) plans, although mean heart dose did not reach statistical significance (Table 4). The skin, defined as a 3-mm rind from the body surface, had a D1 cm³ value that was also significantly greater in the MCBBD plans, but there was no significant difference in the ipsilateral lung V20 Gy (Table 4).

Figure 3 displays EPD (RBE 1.1) and MCBBD plans for a typical patient with immediate breast reconstruction treated with postmastectomy radiation therapy. On the EPD (RBE 1.1) plan, the CTV is covered by at least 90% of prescription (not shown). However, small areas near the chest wall and IMNs are permitted to receive less than prescription dose to spare the heart, lungs, and chest wall (Fig 2A) with the understanding that the biologically effective dose is higher in those locations (Fig 2B). Figure 4A demonstrates an area of high biologic dose identified during MCBBD plan review near the right coronary artery for a different patient undergoing postmastectomy radiation therapy. After reoptimizing, the biologic dose to the heart could be reduced while still maintaining clinically acceptable target coverage (Fig 4B). Setup uncertainty analyses for the CTV, BP, and selected organs at risk are also presented in Table E1 (available online at <https://doi.org/10.1016/j.prro.2019.08.011>).

Discussion

We present our initial experience of breast cancer proton treatment plan evaluation using both biologic and physical dose. The magnitude of the proton RBE at the end of proton range and its impact on tumor control and late tissue effects is uncertain. However, there is compelling evidence that the RBE rises to greater than 1.1 toward the end of proton tracks.^{16–18,36,37} These uncertainties may prove clinically meaningful, such as during elective treatment of the supraclavicular fossa as RBE may be increased within critical structures like the BP. Therefore, when evaluating the quality of proton treatment plans of all patients treated at our institution, physicians and physicists not only assess EPD (RBE 1.1) and MCPD (RBE 1.1) plans, which assume a constant proton RBE of 1.1 relative to high-energy photons, but also assess a GPU-based MCBD model that assumes a linear relationship between dose-averaged LET and biologic dose.

In our photon breast cancer radiation therapy practice, we do not constrain the BP for standard adjuvant prescriptions, such as 50 Gy in 25 fractions, as the tolerance of the BP is generally felt to exceed the hot spots observed on these plans. By the same rationale, we did not initially require the BP to be contoured as an organ at risk when we began treating patients in our breast cancer pencil beam scanning proton therapy program as the physical dose heterogeneity of breast cancer proton plans was comparable, if not improved, relative to that observed with 3-dimensional conformal photon radiation therapy. However, when assessing the MCBD modelled dose to the BP in an initial cohort of patients treated with IMPT, we grew concerned at the possibility that our treatments could be placing patients at higher risk of brachial plexopathy than anticipated based on the BP dosimetry visualized on the EPD (and MCPD) plans. For example, in the first 13 patients treated with proton post-mastectomy radiation therapy at our institution (cohort A), the Dmax to the BP on the MCBD plans ranged as high as 130% of a 50-Gy prescription. Assuming an α/β ratio of 2 for late effects, this BP MCBD Dmax is 75 Gy in 2 Gy fractions, far higher than we would consider clinically acceptable in photon therapy planning for an elective treatment.^{38,39} Our concern was further heightened as we were embarking on a randomized trial of conventional versus hypofractionated pencil beam scanning proton therapy, and larger doses per fraction have previously been associated with risk of brachial plexopathy.^{22,40} Therefore, we implemented physical and biologic dose constraints for the BP for patients undergoing proton regional nodal irradiation. Here, we show that application of these BP constraints has only a small, and likely clinically negligible, impact on CTV coverage. We further highlight areas of high LET in postmastectomy radiation therapy planning, namely the heart and the IMN CTV. For example, the maximum heart dose was approximately 30% higher for the MCBD relative to the EPD (RBE 1.1) and MCPD (RBE 1.1) plans, and the IMN CTV was routinely an area of high LET and RBE. Further investigation is needed to determine the acute and late functional impact of small volumes of the heart being exposed to high-LET proton therapy. Nevertheless, the importance of IMN coverage may vary from case to case based upon patient and disease characteristics.^{10,11} We therefore submit that consideration of LET and RBE heterogeneity can be of value to physicians in breast cancer planning as they make clinical judgments balancing normal tissue sparing and target coverage in an attempt to optimize the therapeutic ratio.

We recognize there are numerous RBE uncertainties and that the MCBBD model used in our practice provides only an estimate of RBE and is not validated by clinical data, a potential limitation of the study.³¹ For example, our model does not take into consideration potential RBE variations with dose or different endpoints of interest such as tumor control or normal tissue complication probability.⁴¹ However, our MCBBD model approximates previously published models derived from fits to in vitro cell survival data (Fig 1).³¹

Increasing evidence suggests that biologic range extension can have important clinical consequences.^{14,42} Treatment planning to mitigate areas of high LET and RBE on the brain stem to reduce brain stem necrosis risk has been an area of focus due to the potentially devastating morbidity caused by each event.^{43–45} In breast cancer, Underwood et al recently found that proton therapy patients had more late-phase pulmonary radiographic changes per Gy (RBE 1.1) than patients treated with photon therapy.²⁰

At present, commercial treatment planning systems are not available to model variations in proton RBE. Still, our findings suggest that limiting hot spots and areas of high LET on the brachial plexus and in the vicinity of the heart at a minimum may be prudent strategies to consider as proton therapy technologies and practices evolve. We also attempt to limit hot spots on the ribs and chest wall without significantly compromising target coverage of the posterior chest wall CTV given the characteristic high LET in that region as protons come to a stop before reaching the lungs (Fig 3B). Notably, we allow BP constraints to be exceeded at physician discretion on a case-by-case basis, such as scenarios where a nodal boost is indicated in the vicinity of the BP.

We are prospectively collecting data on patient-reported arm symptoms. A limitation of the study is the relatively short follow-up as brachial plexopathy can occur years out from treatment. Collection and analysis of long-term treatment outcomes of large numbers of patients across multiple institutions and additional in vitro and in vivo preclinical studies will ultimately be needed to help optimize the use of variable RBE values in proton therapy treatment planning.

Conclusions

In conclusion, physical and biologic dose constraints can be implemented without significantly affecting target coverage of patients undergoing postmastectomy and regional nodal IMPT for breast cancer. The BP should be considered an organ at risk, and RBE heterogeneity should be an important consideration in breast cancer proton treatment planning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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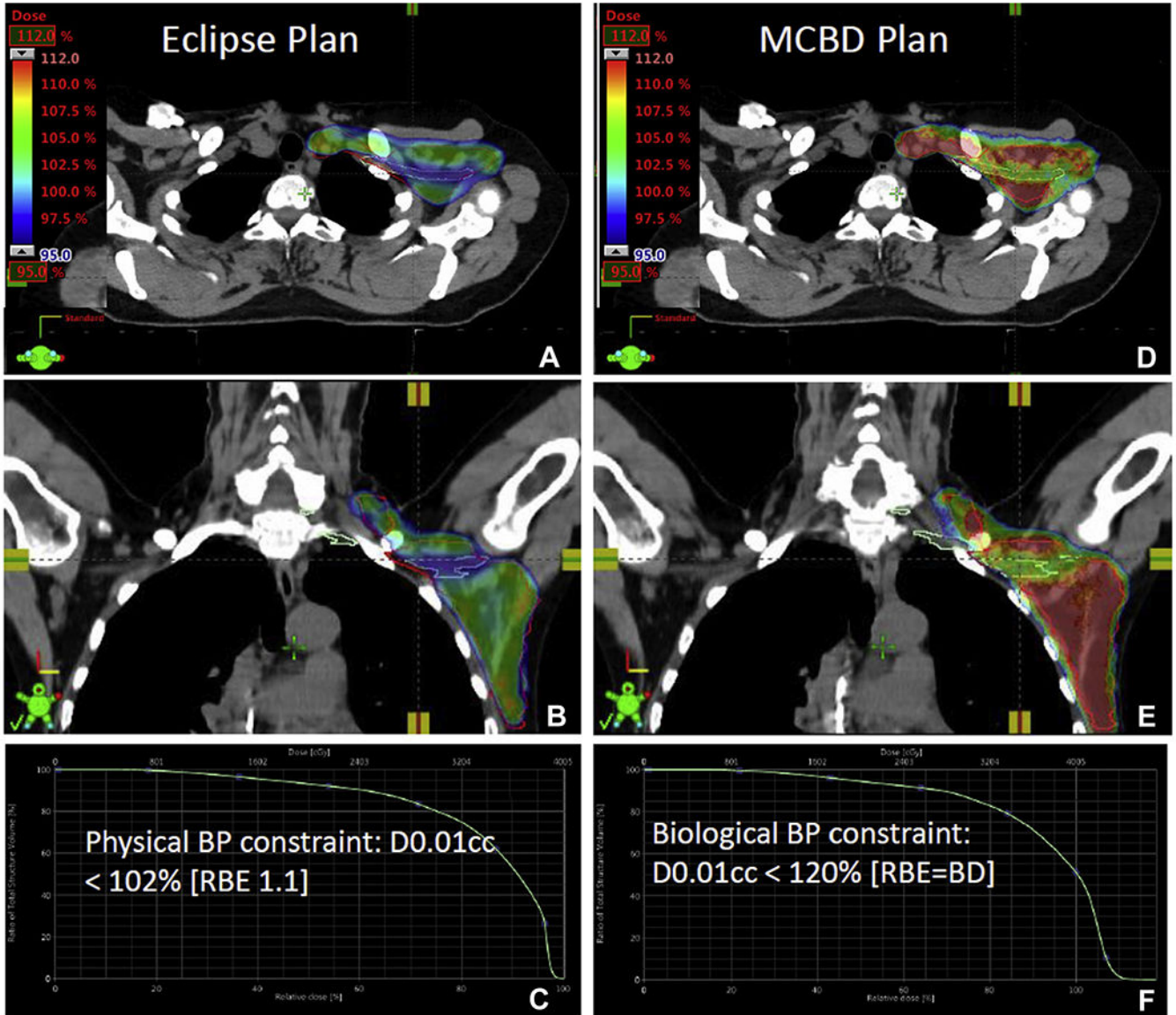


Figure 1. (A, D) Axial and (B, E) coronal color wash images demonstrating constraining of the BP on the (A, B) Eclipse physical dose (RBE 1.1) and the (D, E) in-house MCB simulation for a patient undergoing postmastectomy radiation therapy for left-breast cancer. The MCB assumes a linear relationship between RBE and linear energy transfer (product of RBE and Monte Carlo physical dose = biologic dose). (C, F) Dose-volume histogram demonstrating the BP dose achieved with the physical BP constraint and the biologic BP constraint for the (C) Eclipse physical dose and (F) MCB plans. *Abbreviations:* BP = brachial plexus; MCB = Monte Carlo biologic dose; RBE = relative biologic effectiveness.

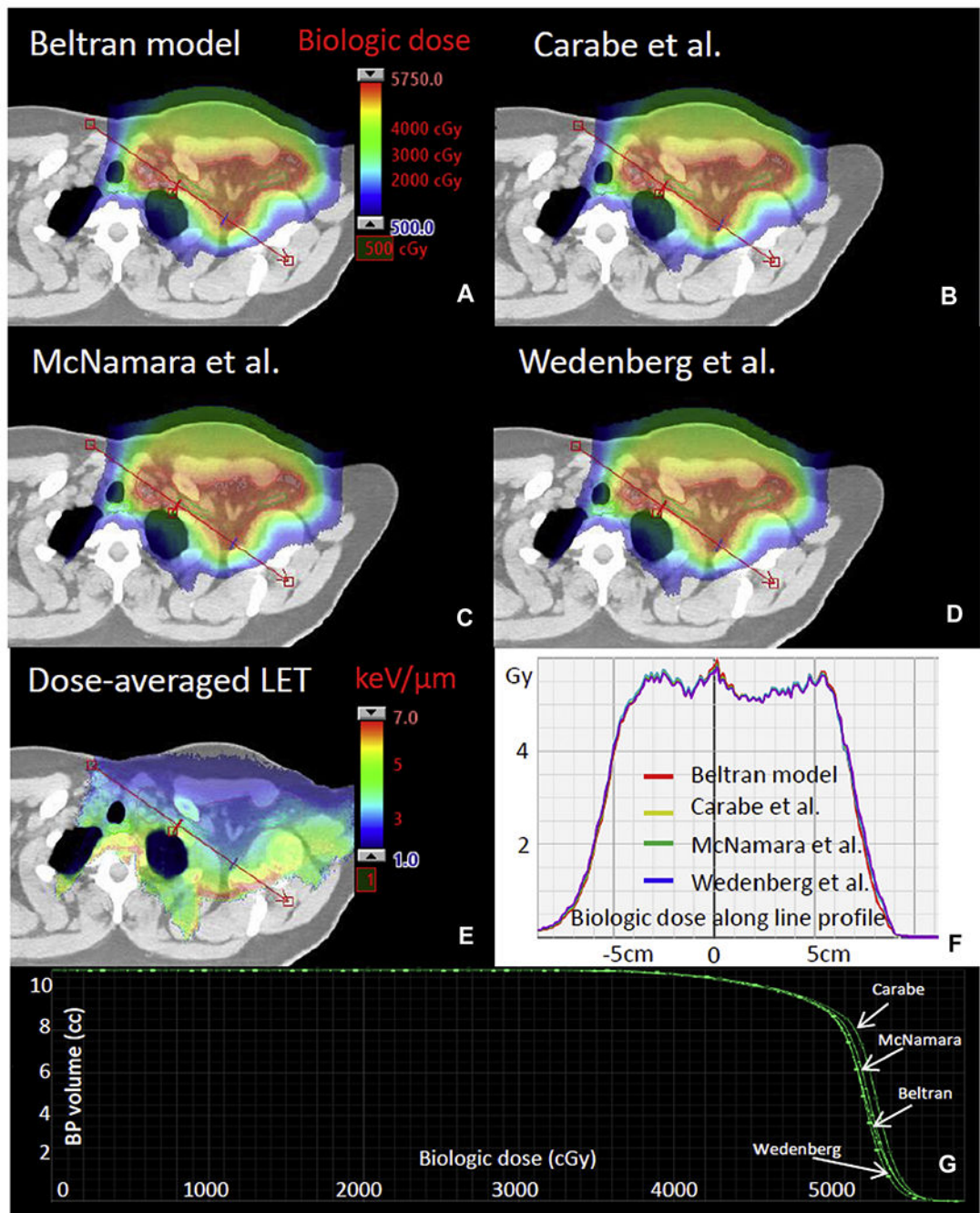


Figure 2.

Axial color wash images demonstrating comparable biologic dose profiles for the (A) Beltran model³⁰ used in this study to previously published models by (B) Carabe et al.,³² (C) McNamara et al.,³⁴ and (D) Wedenberg et al.³³ $\alpha/\beta = 2$ Gy was used for a prescription of 50 Gy in 25 fractions. Clinical target volume (red) and brachial plexus (green) are displayed. (E) The dose-averaged linear energy transfer, (F) the biologic dose line profile for (A-E), and (G) the brachial plexus dose-volume histogram for each model are also shown.

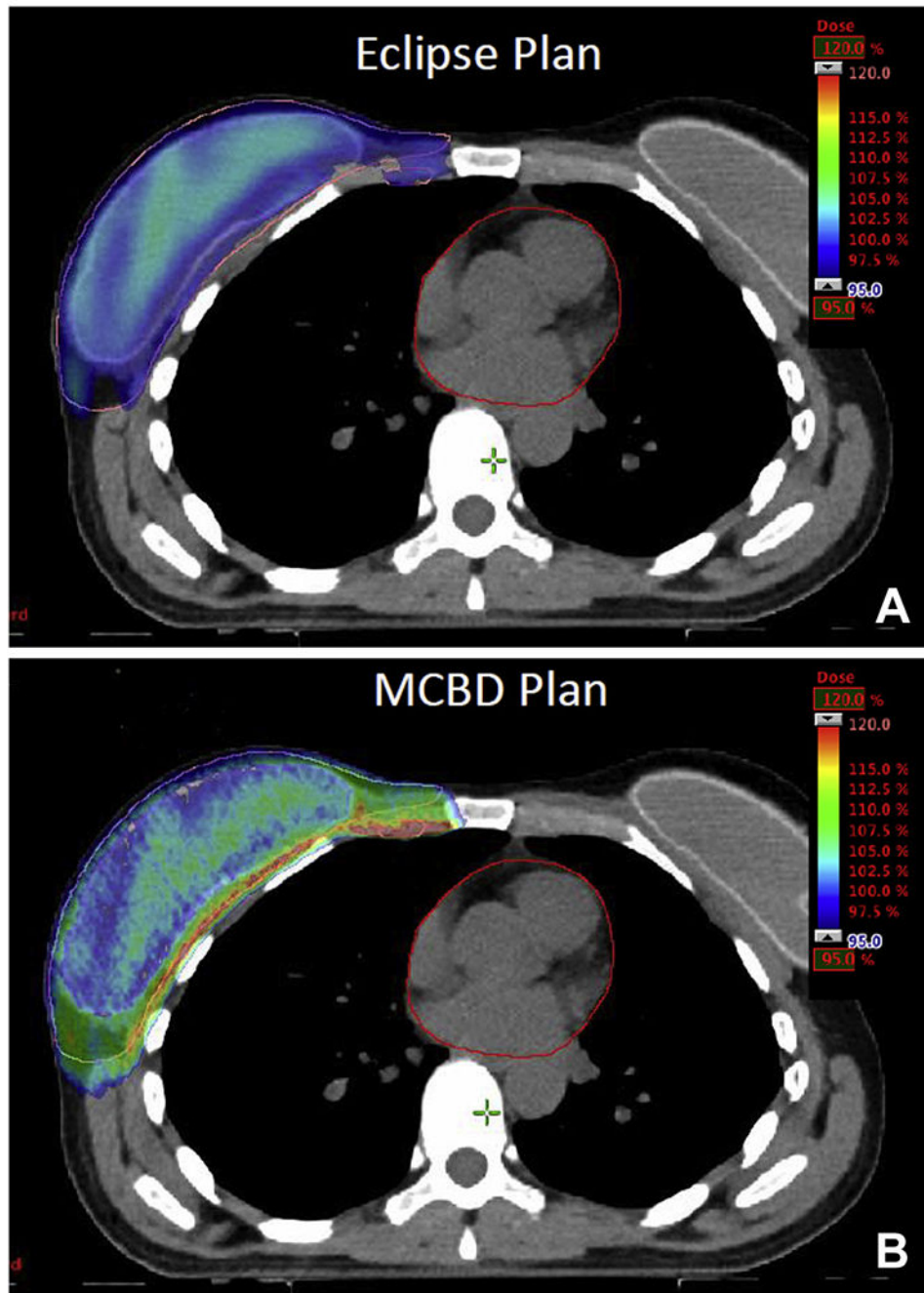


Figure 3. Axial CT images displaying (A) Eclipse physical dose (relative biologic effectiveness 1.1) and (B) Monte Carlo biologic dose 95% to 120% dose color wash images for a patient with immediate breast reconstruction undergoing postmastectomy radiation therapy. (A) Areas of breakup of prescription dose are permitted near the chest wall and internal mammary nodes to reduce the dose to the heart, lungs, and chest wall. (B) The same areas display high biologic dose when linear energy transfer is taken into consideration in the Monte Carlo biologic dose plan.

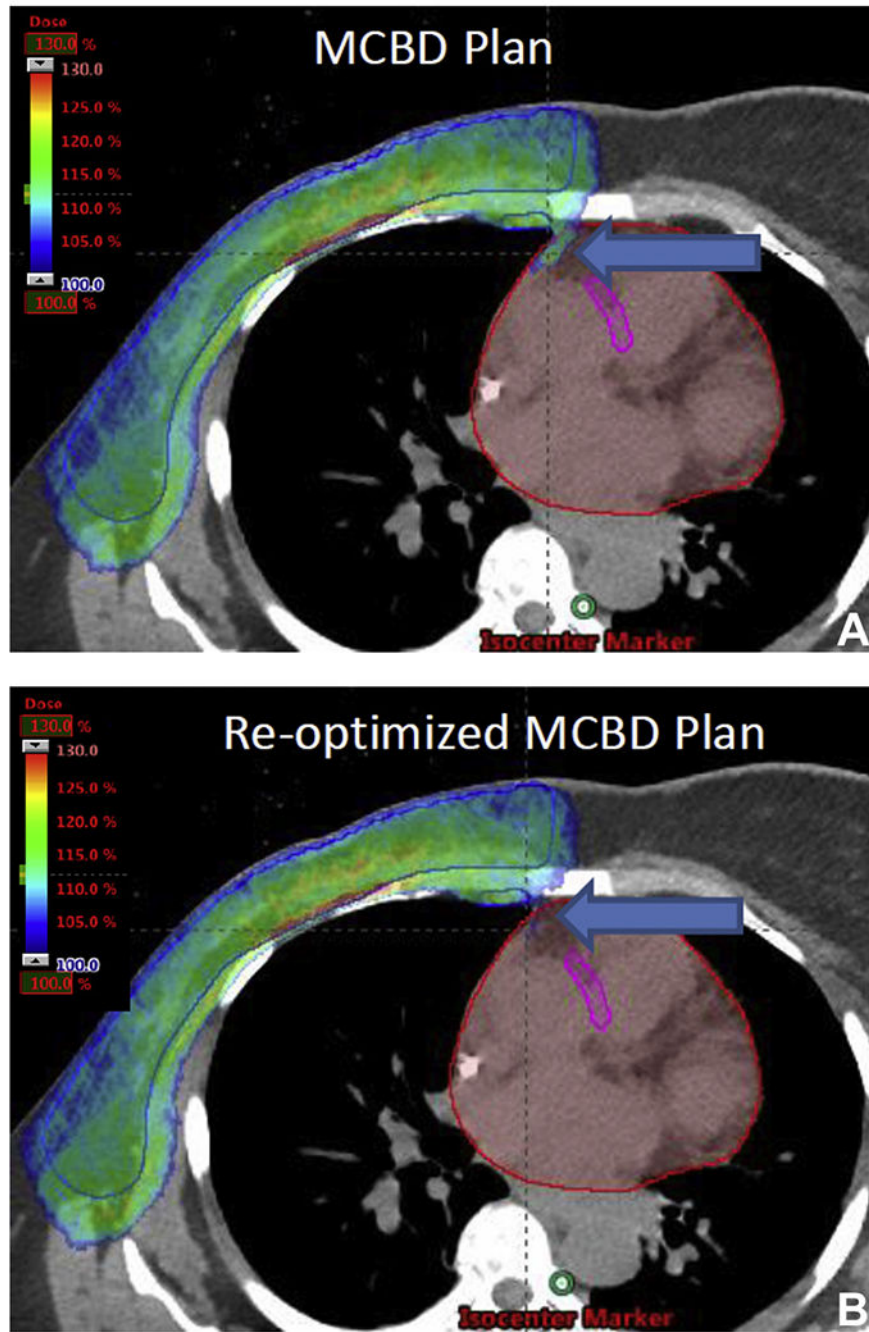


Figure 4. Axial computed tomography images displaying the Monte Carlo biologic dose simulation 100% to 130% dose color wash. (A) On plan review, an area of high biologic dose was demonstrated on the heart in the vicinity of the right coronary artery. (B) Therefore, the plan was reoptimized, removing the area of high biologic dose from the heart while maintaining excellent target coverage of the chest wall and internal mammary nodes.

Table 1

Patient characteristics

Variable	Cohort A	Cohort B	P Value
No.	13	38	
Age, y (IQR)	47 (38-59)	57 (48-65)	.03
Laterality, no. (%)			
Left	11 (92)	21 (55)	
Right	1 (8)	17 (45)	
Stage, no. (%)			
2	2(15)	20 (53)	.02
3	10 (7)	18 (47)	
Recurrent	1 (8)	0 (0)	
Grade, no. (%)			
1	1 (8)	1 (3)	.06
2	4(31)	25 (66)	
3	8 (62)	12 (32)	
ER+, no. (%)	8 (62)	28 (74)	.41
PR+, no. (%)	8 (62)	30 (79)	.21
HER-2+, no. (%)	2(17)	8(21)	.74

Abbreviations: ER = estrogen receptor; HER-2 = human epidermal growth factor receptor 2; IQR = interquartile range; PR = progesterone receptor.

Table 2

Summary of achieved CTV and brachial plexus dosimetric parameters for cohort A and cohort B*

Target organ	DVH parameter	EPD (RBE 1.1)			MCPD (RBE 1.1)			MCBD		
		Cohort A	Cohort B	P Value	Cohort A	Cohort B	P Value	Cohort A	Cohort B	P Value
CTV	D95% (%)	99 (98-100)	97 (95-98)	.0002	99 (98-100)	97 (96-98)	.0404	103 (101-106)	101 (100-103)	.0854
Brachial plexus	D0.01 cm ³ (%)	107 (106-107)	100 (99-102)	<.001	111 (110-112)	103 (102-104)	<.001	128 (126-133)	116 (114-118)	<.001

Abbreviations: CTV = clinical target volume; D0.01 cm³ = 0.01 cm³ of the volume received this dose or more; D95% = 95% of the volume received this dose or more; DVH = dose-volume histogram; EPD = Eclipse physical dose; IQR = interquartile range; MCPD = Monte Carlo biologic dose; MCBD = Monte Carlo physical dose; RBE = relative biologic effectiveness; V20 Gy = the volume receiving 20 Gy or more.

* Reported as median percentage (IQR).

Table 3

Patient-reported arm symptoms at 3 mo compared with baseline

Lift items over 10 pounds with your affected arm			
	Cohort A	Cohort B	P value*
No. [†]	9	32	
Mean difference from baseline	-1.22	-1.44	.82
Reach or extend your arm above shoulder level			
	Cohort A	Cohort B	P value*
No. [†]	7	32	
Mean difference from baseline	-0.57	-0.72	.80
Bend and straighten your affected arm			
	Cohort A	Cohort B	P value*
No. [†]	11	32	
Mean difference from baseline	-0.45	0.03	.39
Numbness or a tingling sensation in the arm on the side that was treated			
	Cohort A	Cohort B	P value*
No. [†]	9	32	
Mean difference from baseline	1.11	0.47	.65

* Welch—Satterthwaite *t* test *P* value.[†]No. = Patients who answered both the baseline and 3 month post-treatment surveys.

Table 4

Summary of achieved IMN and organs at risk dosimetric parameters for the entire cohort^{*}

Target organ	DVH parameter	EPD (RBE 1.1)	MCPD (RBE 1.1)	MCBD	MCPD vs MCBD P value [‡]
IMN	D95%, %	96 (93-98)	94 (93-97)	112 (109-114)	<.0001
Heart	Dmax, %	67 (44-90)	66 (46-93)	89 (59-117)	.002
Heart	Mean, Gy (RBE)	0.5 (0.3-0.8)	0.5 (0.4-1.0)	0.7 (0.5-1.2)	.16
Ipsilateral lung	V20, Gy (RBE), %	11 (7-15)	11 (7-15)	10 (6-14)	.41
Skin [‡]	D1 cm ³ , %	103 (100-104)	104 (102-106)	111 (107-115)	.02

Abbreviations: D1 cm³ = 1 cm³ of the volume received this dose or more; D95% = 95% of the volume receives this dose or more; DVH = dose-volume histogram; EPD = Eclipse physical dose; IMN = internal mammary node; IQR = interquartile range; MCBD = Monte Carlo biologic dose; MCPD = Monte Carlo physical dose; RBE = relative biologic effectiveness; V20 Gy = the volume receiving 20 Gy or more.

^{*} Reported as median percentage (IQR).

[‡] P-values are for the comparison between the MCPD and MCBD plans.

[‡] Skin is defined as the first 3 mm of tissue under the body surface.