Knowledge-Based Volumetric Modulated Arc Therapy Treatment Planning for Breast Cancer

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Abstract

Purpose: To create and to validate knowledge-based volumetric modulated arc therapy (VMAT) models for breast cancer treatments without lymph node irradiation. Materials and Methods: One hundred VMAT-based breast plans (manual plans [MP]) were selected to create two knowledge-based VMAT models (breast left and breast right) using RapidPlan™. The plans were generated on Eclipse v15.5 (Varian Medical Systems, Palo Alto, CA) with 6 MV of a Novalis Tx equipped with a high-resolution multileaf collimator. The models were verified based on goodness-of-fit statistics using the coefficients of determination ($R^2$) and Chi-square ($\chi^2$), and the goodness-of-estimation statistics through the mean square error (MSE). Geometrical and dosimetric constraints were identified and removed from the RP models using statistical evaluation metrics and plots. For validation, 20 plans that integrate the models and 20 plans that do not were reoptimized with RP (closed and opened validation). Dosimetric parameters of interest were used to compare MP versus RP plans for the Heart, Homolateral_Lung, Contralateral_Lung, and Contralateral_Breast. Optimization planning time and user independency were also analyzed. Results: The most unfavorable results of $R^2$ in both models for the organs at risk were as follows: for Contralateral_Lung 0.51 in RP right breast (RP_RB) and for Heart 0.60 in RP left breast (RP_LB). The most unfavorable results of $\chi^2$ test were: for Contralateral_Breast 1.02 in RP_RB and for Heart 1.03 in RP_LB. These goodness-of-fit results show that no overfitting occurred in either of the models. There were no unfavorable results of mean square error (MSE, all < 0.05) in any of the two models. These goodness-of-estimation results show that the models have good estimation power. For closed validation, significant differences were found in RP_RB for Homolateral_Lung (all $P \leq 0.001$), and in the RP_LB differences were found for the heart (all $P \leq 0.04$) and for Homolateral_Lung (all $P \leq 0.022$). For open validation, no statistically significant differences were obtained in either of the models. RP models had little impact on reducing optimization planning times for expert planners; nevertheless, the result showed a 30% reduction time for beginner planners. The use of RP models generates high-quality plans, without differences from the planner experience. Conclusion: Two RP models for breast cancer treatment using VMAT were successfully implemented. The use of RP models for breast cancer reduces the optimization planning time and improves the efficiency of the treatment planning process while ensuring high-quality plans.

Keywords: Breast, RapidArc, RapidPlan

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INTRODUCTION

The intensity-modulated radiotherapy (IMRT) allows to achieve highly conformal dose distributions with the sparing of organs at risk (OARs).[1-2] Several studies demonstrated the dosimetric advantages of intensity-modulated techniques compared with three-dimensional conformal radiotherapy (3DCRT).[3-4] On the other hand, some of the disadvantages of modulated techniques include the increment in total body irradiation with lower doses, sharp dose gradients require image guidance and it is time-consuming and complex procedure.[5] The complexity of inverse planning optimization could generate strongly planner-dependent plans. Volumetric modulated arc therapy (VMAT) is an intensity-modulated technique which improves the treatment efficiency. VMAT technique takes into account the treatment time and monitor units reduction compared to the use of modulated fixed gantry angle beams.[6-12] The commonly used breast radiotherapy treatment plans consist of parallel opposed tangential wedged beams.

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or multiple segments.\textsuperscript{[13]} However, VMAT can be performed for breast plans preserving similar coverage, reaching better planning target volume (PTV) conformity and homogeneity, and higher sparing of homolateral lung and heart.\textsuperscript{[14-16]}

Knowledge-based planning (KBP) has gained a lot of interest in radiation medical physics due to the planning-time reduction and plan quality improvement.\textsuperscript{[17]} RapidPlan\textsuperscript{TM} is a commercial KBP tool implemented in the Varian Eclipse engine (Varian Medical Systems, Palo Alto, CA) treatment planning system. RapidPlan\textsuperscript{TM} (RP) uses site-specific manually optimized plans libraries to estimate the best dose distribution achieved in a new plan.\textsuperscript{[18]} Currently, there are RP-reported models for liver,\textsuperscript{[19]} head-and-neck,\textsuperscript{[20]} lung SBRT,\textsuperscript{[21]} prostate,\textsuperscript{[22]} cervix,\textsuperscript{[23]} and esophagus.\textsuperscript{[24]} These models have shown improvements on treatment plan quality planning time-reduction and quality consistency.

In the particular case of breast treatment planning, the VMAT RP models improve the plan quality throughout many radiation oncology centers.\textsuperscript{[25]} After KBP implementation in a center, any physicist or dosimetrist can generate acceptable breast IMRT plans, regardless of their experience.\textsuperscript{[26]} By the use of hybrid RapidArc\textsuperscript{TM} plan (tangential and three VMAT arcs) in the breast with lymph nodes treatments, the KBP and MP plan quality was comparable, but KBP treatment time was substantially shorter.\textsuperscript{[27]} A 3DCRT RP_LB model was created and used it as a prediction method to determine which patients would benefit from the deep inspiration breath-hold technique.\textsuperscript{[28]}

VMAT breast treatment planning was implemented at our institution since 2016. Immediately, it became evident the dependence of physicist and dosimetrist expertise in plan quality and planning time. Therefore, the use of KBP was proposed. This work shows the RP model implementation and validation for the right breast (RP_RB) and left breast (RP_LB). The work includes the plan quality improvement and consistency and the planning-time reduction.

**Materials and Methods**

**Breast VMAT treatment planning technique**

VMAT treatment plans were generated by the use of RapidArc\textsuperscript{TM} on Eclipse v15.5 (Varian Medical Systems, Palo Alto, CA). The plans consisted of two semi-arcs (clockwise and counterclockwise) of 240 degrees (LB from 300° to 180°, RB from 60° to 180°) with complementary 20° collimator angles. The plans were performed on 6 MV photon beam energy in a Novalis Tx linear accelerator (Varian Medical Systems, Palo Alto, CA-Brainlab AG, Munchen, Germany) equipped with a high definition multileaf collimator.

The clinical institutional breast treatment planning protocol included breast irradiation (CTV_breast) with three dose levels in 20 fractions.\textsuperscript{[29]} The CTV simultaneous integrated boost (CTV_SIB) dose prescription was 5600 cGy, proximal CTV (CTV_proximal) was 4600 cGy and distal CTV (CTV_distal) was 4300 cGy. The PTV consisted of 5 mm CTV expansion in all directions. PTVs were identified according to the AAPM report TG-263\textsuperscript{[30]} nomenclature, as shown in Figure 1a. The sum of all PTVs was generated and named zPTV_Total! The organs at risk (OARs) considered were the right lung, left lung, heart, contralateral breast, spinal cord, bowel, trachea, and esophagus. The dose-volume constraints and the equivalent dose to 200 cGy regimens followed are detailed in Table 1.\textsuperscript{[31]}

The isocenter was placed at the zPTV_Total! center of mass. The plan was based on a reported planning strategy.\textsuperscript{[32]} The strategy consisted of the use of duplicated CT image series (modified_CT and original_CT) for inverse planning and dose calculation, respectively. Both image sets shared the planning structures. The modified_CT included a planning structure (ring) to reduce the contralateral breast and lung dose. The ring was created with 12 mm expansion of the body and the PTVs toward the body external direction along the breast whole extension, as shown in Figure 1b. The created expansion region considered breast motion (pseudo-skin-flash) by the use of Boolean operation. Density of 1 was assigned to

**Table 1: Institutional dose-volume constrains for RapidArc breast treatment planning in 20 fractions**

| Volume                     | Dose constrains                   |
|----------------------------|-----------------------------------|
| PTV_SIB (zPTV_High_5600!)  | 5600 cGy                          |
| (EQD2 6500cGy)             | D95% >5320 cGy                    |
|                            | D2% <6000 cGy                      |
| PTV_proximal (zPTV_Mid_4600!) | 4600 cGy                           |
| (EQD2 4800 cGy)            | D95% >4300 cGy                     |
| PTV_distal (zPTV_Low_4300!) | 4300 cGy                           |
| (EQD2 4430 cGy)            | D95% >4090 cGy                     |
| Homolateral_Lung           |                                   |
| V1000 cGy                  | < 50%                             |
| V2000 cGy                  | < 10%                             |
| V4000 cGy                  | < 3%                              |
| SpinalCord                 |                                   |
| Dmax                       | < 350 cGy (optimal)               |
| Heart                      |                                   |
| V1000 cGy                  | < 8%                              |
| Mean Dose                  | < 350 cGy (left breast)           |
|                            | <150 cGy (right breast)           |
| Liver                      |                                   |
| V2000 cGy                  | < 20%                             |
| Contralateral_Breast       |                                   |
| Dmax                       | < 1000 cGy (optimal)              |
| Mean Dose                  | <200 cGy                          |

PTV: Planning target volume, SIB: simultaneous integrated boost, zPTV: Nomenclature for PTV
this region. Once the inverse planning reached the planning objective, the optimized plan was pasted into the original CT where dose distribution was calculated. The CTVs and PTVs of the original CT were trimmed 5 mm within the body. The anisotropic analytical algorithm and 2.5 mm grid size were used for dose calculation.

**RapidPlan model and patient plan selection**

Detail RP technical aspects have been described in the literature. \[17,33\] RP used site-specific manually optimized treatment MP libraries to get the best dose distribution estimation for a new plan. \[18\] RP provided the estimation by regression analysis to create a statistical model based on geometrical and dosimetric characteristics extracted from MP. The geometrical components of the model took into account target and OARs volume information whether they were inside or outside the MLC and the field overlap. The dosimetrical component provided the dose estimation for a given structure (target or OARs) based on the geometric characteristics described.

The RP model was used in the new plans for target and OARs dose objectives optimization. First, the model brought forward the dose-volume histogram (DVH) estimation took into account upper and lower dose constraints for all structures. The constraints are related to atypical values and influence data.

Fifty VMAT left breast without lymph nodes MP for 20 fractions were selected to create the left breast RP model (RP_LB). Fifty right breasts without lymph nodes MP were chosen for the right breast RP model (RP_RB). Approved and performed in patients MP belonged to our institutional database. The selected MP included different CTV_Breast volumes (V_{CTV_Breast}) to take into account the breast size. The institutional breast size classification considered small breast V_{CTV_Breast} <400 cc, medium breast V_{CTV_Breast} (400 cc, 700 cc), and large breast V_{CTV_Breast} >700 cc.

MP were uploaded and used for RP data extraction (anatomy, field geometry, and dose prescription) and model training (geometrical and dosimetrical correlation).

**Model evaluation and validation**

The atypical and influence data of the RP models were identified by statistics parameters and plots (residual, regression, and in-field DVH) that were included in the RP module. \[18\] The verification of RP models was based on goodness-of-fit statistics by the coefficient of determination (R^2) and Chi-square values (X^2) and the goodness-of-estimation statistics by the MSE. The R^2, X^2 and MSE, statistical tools, are inbuilt in the RP module of the eclipse. R^2 values close to 1 showed a good fit. X^2 values near to 1 meant a good regression model. MSE values close to 0 showed a good estimation capability of the model.

The validation of RP models was performed with 20 random plans (10 RP_LB and 10 RP_RB) included in the initial RP configuration (opened validation) and 20 plans (10 RP_LB and 10 RP_RB) not included in the initial RP configuration (closed validation). \[18,19\] All generated plans with RP not had planner intervention during the optimization process. The final DVHs for MP and RP were compared using the two-tailed student test analysis with P = 0.05 statistical significance. \[134\] The Heart, Homolateral_Lung, and Contralateral_Breast DVH were calculated and compared for 10 MP and RP selected from the opened validation.

**Optimization time and homogeneity**

The RP impact on the optimization time was evaluated in 10 physicists and dosimetrist separated in two groups: experts (5) and beginners (5). Experts group had more than 2 years of experience on VMAT breast treatment planning. The beginners group had <2 years of experience. The optimization in 42 plans with and without RP was performed. The optimization time was measured starting from the optimization start phase until its completion considering intermediate-dose calculations. The plan homogeneity impact was evaluated for RP_RB and MP_RB in eight physicists and dosimetrist, regardless of the expertise. DVH scatter comparison for OARs between MP and RP was studied by Levene’s test with P = 0.05 statistical significance.

**Results**

The RP_RB model included 38% of MP for small breast, 38% for medium breast, and 24% for large breast. The RP_LB model included 30% of MP for small breast, 39% for medium breast and 31% for large breast. No over adjustments ( and ) were observed in the generated models. The largest was 0.51 for the Contralateral_Lung in RP_RB and for the Heart in RP_LB. The smallest was 1.02 for the Contralateral_Breast in RP_RB and for the Heart in RP_LB. MSE were within the acceptable range showing good DVH estimation power (≤0.05). Goodness-of-fit values for Heart, Contralateral_Lung, Homolateral_Lung, and Contralateral_Breast are shown in Table 2 and Supplementary Table 1 for RP_LB and RP_RB, respectively (supplementary material). The results of the above statistical analysis show that both models have good estimation ability and without atypical values. Some examples for in-field DVH, regression, and residual plots for Heart in LB and RB are shown in Figure 2a-f and for Homolateral_Lung in Figure supplement 1a-f.

The opened and closed validation in MP and RP dose distribution for LB and RB were similar and fulfilled the institutional PTVs and OARs dose-volume constraints. An

| Structure            | R^2  | X^2  | MSE   |
|----------------------|------|------|-------|
| Heart                | 0.60 | 1.03 | 0.01  |
| Contralateral_Lung   | 0.30 | 1.04 | 0.00  |
| Homolateral_Lung     | 0.41 | 1.08 | 0.05  |
| Contralateral_Breast | 0.21 | 1.06 | 0.05  |
| MSE: Mean Square Error |     |      |       |
example is shown in Figure 3a-b for RB and LB between MP and RP, respectively.

The closed validation for both RP models showed better PTV dose coverage than MP. Table 3 shows statistically significant differences ($P < 0.001$) for the middle dose level (zCTV_Mid_4600). The opened validation for both RP models did not show statistically significant with MP ($P > 0.071$).

For RB closed validation there was statistically significant difference for Homolateral_Lung ($P \leq 0.001$) in favor to MP. For LB there was statistically significant difference for Heart ($P \leq 0.04$) in favor to RP and for Homolateral_Lung ($P \leq 0.022$) in favor to MP. Tables 3 and 4 show the LB dosimetrical closed and opened validation for MP and RP. Supplementary Tables 2 and 3 show the RB dosimetrical closed and opened validation for MP and RP.

The Heart, Homolateral_Lung, and Contralateral_Breast mean DVH of 10 MP and RP plans were compared and showed no differences, as shown in Figure 4 and Figure Supplement 2 for LB and RB respectively.

The use of RP by expert group of physicists and dosimetrists had little impact on treatment planning times. Nevertheless, there was 30% of reduction time (7 min) for the beginner group, as shown in Table 5.

The use of RP performed plans with similar OARs DVH with respect to MP. The mean DVH scatters for OARs could be reduced using RP compared to MP, regardless of physicists or dosimetrists expertise. The mean LB DVH OARs (Heart, Contralateral_Breast, Contralateral_Lung, and Homolateral_Lung) between MP and RP performed by the beginner and expert group is shown in Figure 5.

RP performed plans with less variance concerning MP, as can be seen in Table 6 where the obtained values for RP are always lower than the corresponding MP values. Table 6 shows LB mean and variance values for Heart (Dmean and D8%), Homolateral_Lung (DS0%,D20% and D10%), Contralateral_Breast (Dmean and D8%), and Contralateral_Lung (DS0%,D20% and D10%).
Table 3: Close validation dosimetric comparison between manual plans and RapidPlan plans for left breast

| Structure          | Parameter          | MP      | RP       | P      |
|--------------------|--------------------|---------|----------|--------|
| zPTV_High_5600!    | D95% [Gy]          | 55.1±0.6| 54.5±0.4| 0.013  |
|                    | D2% [Gy]           | 60.1±0.9| 60.0±0.5| 0.769  |
| zPTV_Mid_4600!     | D95% [Gy]          | 44.6±0.5| 45.8±0.8| <0.001 |
| zPTV_Low_4300!     | D95% [Gy]          | 42.1±0.5| 42.0±0.7| 0.006  |
| Heart              | D8% [Gy]           | 5.8±1.2 | 5.0±0.6 | 0.040  |
|                    | Mean [Gy]          | 3.4±0.5 | 3.1±0.4 | 0.019  |
| SpinalCord         | Max [Gy]           | 4.2±0.6 | 3.9±0.3 | 0.126  |
| Homolateral_Lung   | D50% [Gy]          | 5.9±1.1 | 6.4±0.7 | 0.006  |
|                    | D20% [Gy]          | 11.1±1.2| 12.0±0.7| 0.022  |
|                    | D10% [Gy]          | 15.8±1.4| 17.0±1.5| 0.015  |
| Contralateral_Lung | D20% [Gy]          | 3.7±0.4 | 3.5±0.3 | 0.118  |
|                    | D10% [Gy]          | 4.8±0.6 | 4.9±0.8 | 0.667  |
| Contralateral_Breast | Max [Gy]        | 8.6±1.7 | 11.1±1.4| 0.006  |
|                    | Mean [Gy]          | 2.2±0.3 | 2.4±0.1 | 0.776  |

Plans belonging to close validation were included in the RapidPlan model. MP: Manual plan, RP: RapidPlan plan, zPTV: Nomenclature for PTV.

Table 4: Open validation dosimetric comparison between manual plans and RapidPlan plans for left breast

| Structure          | Parameter          | MP      | RP       | P      |
|--------------------|--------------------|---------|----------|--------|
| zPTV_High_5600!    | D95% [Gy]          | 54.6±0.7| 54.6±0.7| 0.176  |
|                    | D2% [Gy]           | 60.2±0.4| 60.0±0.4| 0.593  |
| zPTV_Mid_4600!     | D95% [Gy]          | 44.8±0.4| 44.6±0.5| <0.071 |
| zPTV_Low_4300!     | D95% [Gy]          | 42.1±0.4| 42.0±0.5| 0.480  |
| Heart              | D8% [Gy]           | 5.1±1.0 | 4.8±0.8 | 0.433  |
|                    | Mean [Gy]          | 2.8±0.6 | 2.7±0.5 | 0.410  |
| SpinalCord         | Max [Gy]           | 3.6±0.4 | 3.8±0.4 | 0.323  |
| Homolateral_Lung   | D50% [Gy]          | 5.9±0.8 | 6.0±0.6 | 0.799  |
|                    | D20% [Gy]          | 11.5±1.5| 11.6±1.2| 0.828  |
|                    | D10% [Gy]          | 16.2±2.2| 16.1±1.9| 0.686  |
| Contralateral_Lung | D20% [Gy]          | 3.3±0.5 | 3.5±0.5 | 0.003  |
|                    | D10% [Gy]          | 4.4±0.7 | 4.8±0.7 | 0.003  |
| Contralateral_Breast | Max [Gy]      | 9.7±2.7 | 10.0±2.5| 0.441  |
|                    | Mean [Gy]          | 2.2±0.3 | 2.3±0.3 | 0.156  |

Plans belonging to open validation were not included in the RapidPlan model. MP: Manual plan, RP: RapidPlan plan, zPTV: Nomenclature for PTV.

Table 5: Impact of using RapidPlan models on treatment planning times for beginners and expert planners

| Planning time (min) | Beginner planner | Expert planner |
|---------------------|------------------|----------------|
|                     | MP    | RP  | MP    | RP  |
| Minimum             | 12.4  | 11.2| 10.5  | 10.2|
| Maximum             | 35.4  | 22.0| 30.5  | 23.2|
| Mean                | 22.1  | 15.4| 16.8  | 15.4|
| Standard deviation  | 6.0   | 3.8 | 4.7   | 3.3 |
| Difference           | 6.7   | 1.0 |       |     |
| Difference (%)       | -30.3 | -8.4|       |     |

MP: Manual plans, RP: RapidPlan plans

Discussion

Two RapidPlan models for left and right breast cancer without lymph node irradiation were created using the VMAT treatment technique. Each RP model was created using fifty plans done by planners of our Institution (MPs), and all of them fulfill the Institutional dose-volume constraints for PTVs and OARs. The models’ variability was considered in the models, as plans for different breast volumes were included. Even when the minimum number of plans require for creating an RP model in Eclipse is twenty, breast sizes variability induced us to include fifty plans in each model. The number of MPs included in the RPs models is similar to the used by others authors in different treatment sites.[17,20,33] The statistical tools used in this paper to verify the goodness of the models are inbuilt into Eclipse and help detect atypical values. Obtained values of $R^2$, $\chi^2$, and MSE for the two RP models were comparable with values reported by other authors[35] and[36] which show that RP models generated good dosimetric results. Close and open RP validation confirms that the RP models, verified by the cited statistical tools, can generate plans comparable to MPs of beginners or expert planners. The last result becomes more significant due to there was no human intervention during the optimization process with RP. Furthermore, the use of
Table 6: Comparison of planning homogeneity between manual plan versus RapidPlan plan for the left breast

| Structure             | Parameter | Plan   | Mean (Gy) | Variance (Gy²) | Levene Test, P | t-test* | P0     | Mean difference |
|-----------------------|-----------|--------|-----------|----------------|----------------|---------|--------|----------------|
| Heart                 | D8%       | MP     | 6.19      | 21.40          | 0.026          | 0.282   | 0.039  |
| Heart                 |           | RP     | 6.15      | 0.09           |                |         |        |                |
| Heart                 | Mean      | MP     | 3.79      | 11.91          | 0.001          | 0.205   | 0.165  |
| Homolateral_Lung      | D50%      | MP     | 6.24      | 0.63           | 0.049          | 0.381   | 0.315  |
| Homolateral_Lung      | D20%      | MP     | 11.37     | 3.00           | 0.014          | 0.124   | 0.865  |
| Homolateral_Lung      | D10%      | MP     | 16.12     | 4.21           | 0.036          | 0.196   | 0.398  |
|                      |           | RP     | 14.72     | 0.54           |                |         |        |                |
| Contralateral_Lung    | D20%      | MP     | 3.12      | 0.43           | 0.014          | 0.737   | 0.173  |
| Contralateral_Lung    | D10%      | MP     | 3.94      | 0.74           | 0.008          | 0.476   | 0.185  |
|                      |           | RP     | 3.66      | 0.04           |                |         |        |                |
| Contralateral_Breast  | Max       | MP     | 7.22      | 1.15           | 0.004          | 0.193   | -0.635 |
|                      |           | RP     | 7.85      | 0.04           |                |         |        |                |
| Contralateral_Breast  | Mean      | MP     | 2.09      | 0.21           | 0.031          | 0.145   | -0.155 |
|                      |           | RP     | 2.25      | 0.01           |                |         |        |                |

*Equality of means. †Two-tailed t-test and equal variance are not assumed. MP: Manual plans, RP: RapidPlan plans

Figure 5: Average DVH comparison for left breast (LB) between manual plans (MP) and RapidPlan plans (RPs), executed by beginner and expert planners. Heart, Contralateral_Breast, Contralateral_Lung, and Homolateral_Lung

RP reduces the treatment planning time on beginner planners and increases the homogeneity of plans results beyond the planner’s expertise.

CONCLUSION

Two VMAT RP models for breast treatment for 20 fractions were successfully implemented to the three-dose levels protocol. We conclude that the RP plans performed are dosimetrically equivalent to MP generated by expert physicists and dosimetrists. The same procedure could be used to implement VMAT RP models with different dose prescription protocols.

The use of RP models for breast cancer reduces the optimization planning time and improves the efficiency of the treatment planning process while ensuring high-quality plans. However, longer time and experience in the use of RP are necessary to confirm the results shown in this study. Both RP models can be requested from our Institutional website (www.institutozunino.org).

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Conflicts of interest
There are no conflicts of interest.

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Figure Supplement 1: (a, c, e) In-field DVH, regression and residual plots for Homolateral_Lung in RapidPlan Right Breast model (RP_RB) and (b, d, f) in RapidPlan left breast model (RP_LB)

Supplementary Table 1: Goodness-of-fit $R^2$ and $\chi^2$ and goodness-of-estimation Mean Square Error for RapidPlan right breast

| Structure            | $R^2$ | $\chi^2$ | MSE  |
|----------------------|-------|----------|------|
| Heart                | 0.47  | 1.09     | 0.05 |
| Contralateral_Lung   | 0.51  | 1.08     | 0.00 |
| Homolateral_Lung     | 0.41  | 1.06     | 0.05 |
| Contralateral_Breast | 0.09  | 1.02     | 0.04 |

MSE: Mean Square Error

Figure Supplement 2: Right breast (RB) average DVH for ten plans using manual plans and RapidPlans for Heart, Homolateral_Lung and Contralateral_Breast
### Supplementary Table 2: Close validation dosimetric comparison between manual plans and RapidPlan plans for right breast

| Structure          | Parameter | MP     | RP     | P   |
|--------------------|-----------|--------|--------|-----|
| zPTV_High_5600!    | D95% [Gy] | 54.6±0.4 | 54.4±0.3 | 0.066 |
|                    | D2% [Gy]  | 60.2±0.7 | 59.8±0.4 | 0.055 |
| zPTV_Mid_4600!     | D95% [Gy] | 44.2±0.4 | 44.7±0.4 | 0.007 |
| zPTV_Low_4300!     | D95% [Gy] | 42.1±0.4 | 41.9±0.3 | 0.154 |
| Heart              | D8% [Gy]  | 4.7±0.5  | 4.8±0.6  | 0.718 |
|                    | Mean [Gy] | 2.4±0.1  | 2.4±0.3  | 0.907 |
| SpinalCord         | Max [Gy]  | 3.8±0.2  | 4.0±0.5  | 0.245 |
| Homolateral_Lung   | D50% [Gy] | 6.8±0.3  | 7.1±0.4  | 0.001 |
|                    | D20% [Gy] | 11.7±0.6 | 12.1±0.6 | 0.001 |
|                    | D10% [Gy] | 15.8±0.9 | 16.5±1.1 | <0.001 |
| Contralateral_Lung | D20% [Gy] | 3.0±0.4  | 2.8±0.2  | 0.131 |
|                    | D10% [Gy] | 3.9±0.6  | 3.7±0.4  | 0.386 |
| Contralateral_Breast | Max [Gy] | 8.9±1.6  | 8.6±2.0  | 0.410 |
|                    | Mean [Gy] | 2.10±0.2 | 2.1±0.1  | 0.578 |

MP: Manual plan, RP: RapidPlan plan

### Supplementary Table 3: Open validation dosimetric comparison between manual plans and RapidPlan plans for right breast

| Structure          | Parameter | MP     | RP     | P   |
|--------------------|-----------|--------|--------|-----|
| zPTV_High_5600!    | D95% [Gy] | 54.5±0.7 | 54.5±0.7 | 0.161 |
|                    | D2% [Gy]  | 60.1±0.5 | 59.8±0.8 | 0.244 |
| zPTV_Mid_4600!     | D95% [Gy] | 44.6±0.7 | 44.4±0.6 | 0.356 |
| zPTV_Low_4300!     | D95% [Gy] | 41.9±0.6 | 41.5±0.6 | 0.059 |
| Heart              | D8% [Gy]  | 2.5±0.5  | 2.7±0.5  | 0.467 |
|                    | Mean [Gy] | 1.5±0.3  | 1.6±0.3  | 0.582 |
| SpinalCord         | Max [Gy]  | 3.7±0.5  | 4.0±0.4  | 0.117 |
| Homolateral_Lung   | D50% [Gy] | 6.9±0.7  | 7.1±0.4  | 0.581 |
|                    | D20% [Gy] | 12.3±1.7 | 12.1±1.2 | 0.575 |
|                    | D10% [Gy] | 17.2±2.3 | 17.1±1.9 | 0.864 |
| Contralateral_Lung | D20% [Gy] | 2.9±0.3  | 2.7±0.3  | 0.124 |
|                    | D10% [Gy] | 3.8±0.6  | 3.6±0.7  | 0.188 |
| Contralateral_Breast | Max [Gy] | 9.5±2.0  | 10.0±2.2 | 0.078 |
|                    | Mean [Gy] | 2.4±0.4  | 2.2±0.3  | 0.207 |

MP: Manual plan, RP: RapidPlan plan