Am J Transl Res 2022;14(11):7985-7993
www.ajtr.org /ISSN:1943-8141/AJTR0144660

Original Article

Dosimetric advantages of robust optimization combined with flattening filter free in treating cancer of the left breast

Hongying Luo[1*], Jianlin Lou[2*], Wei Feng[3], Guoping Shan[3], Kainan Shao[3], Yiwei Yang[3], Jianliang Zhou[1], Shengye Wang[3]

[1]University of South China, School of Nuclear Science and Technology, Hengyang 421001, Hunan, China; [2]Department of Head & Neck Surgery, The Cancer Hospital of The University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou 310022, Zhejiang, China; [3]Department of Radiation Physics, The Cancer Hospital of The University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou 310022, Zhejiang, China. [*]Equal contributors.

Received June 9, 2022; Accepted September 16, 2022; Epub November 15, 2022; Published November 30, 2022

Abstract: Objective: By comparing the target dose distribution with or without the robust optimization, the dosimetric advantages of robust optimization and flattening filter free (FFF) in radiation therapy for postmastectomy cancer of the left breast was explored when part of the chest wall target was moved out in case of respiratory motion. Materials and methods: This is a retrospective study. The data of 21 postmastectomy patients with cancer of the left breast from 2019 to 2020 were retrospectively collected. The planned target volume (PTV) dose was prescribed 50 Gy/25 fractions and the treatment plans were designed using 6 MV FFF X ray and volumetric modulated arc therapy (VMAT) technology in RayStation treatment planning system (TPS), with and without robust optimization. The movement of the target area of the internal chest wall (0.50 cm) caused by respiratory movement was simulated by moving the isocenter of the beams. Results: When the chest wall target moved outward, the PTV target area D_{98}, D_{95}, D_{2}, conformity index (CI) and homogeneity index (HI) with robust optimization were better than those without robust optimization. The coverage rate of Planned Target Volume-Chest (PTV-T) V_{50} with robust optimization was significantly higher than that with no-robust optimization ($P<0.001$). Clinical target volume (CTV) V_{50} coverage with robust optimization was 14.49% higher than that with no-robust optimization. In terms of organ-at-risk parameters, the average spinal cord dose of the plan with robust optimization was 13.19% lower than that of the plan with no-robust optimization, and the Lung-L V_{5} of the plan with no-robust optimization was slightly (1.94%) lower than that of the plan with robust optimization. There was no significant difference in machine execution efficiency between the two groups ($P>0.05$). Conclusions: Robust optimization could be adopted in the postoperative radiotherapy planning for cancer in the left breast, for it ensures that the target dose coverage and the dose limit of organ-at-risk still meet the clinical requirements under condition of chest wall displacement caused by respiratory movement.

Keywords: Robust optimization, postoperative left breast cancer, flatten filter free mode, volumetric modulated arc therapy, dosimetric characteristics

Introduction

Breast cancer is one of the main malignant tumors leading to female deaths worldwide, and its incidence has been increasing in recent years [1]. Radiation therapy for postoperative patients with cancer of the left breast is suitable for patients with high risk of recurrence. Clinical target volume (CTV) is extremely complex, including high-risk recurrence areas and high-risk lymphatic drainage areas, especially including the chest wall, regional lymph nodes, supraclavicular area, axillary and internal mammary areas. Post-mastectomy radiotherapy (PMRT) for patients with breast cancer can reduce the risk of locoregional recurrence (LRR), and improvement in locoregional control can impact overall survival (OS) [2].

Intensity-modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) have been developed and used for radiation

therapy of breast cancer, both in dosimetry research and clinical trials [3-6]. They have the advantage of fast generation of treatment plans, which meet the clinical target dose coverage and protect organs at risk (OARs) [7, 8] and can even achieve better dosimetric results than Conventional Tangential Field Conformal radiotherapy techniques [9]. Radiation therapy may induce heart diseases and cardiovascular events caused by the definite effects of radiation. Intended to reduce patients' side effects, we introduced a flattening filter free (FFF) mode supported by Varian TrueBeam linear accelerator (Varian Medical System, CA). It has a larger range of modulation in breast cancer radiotherapy plans with partial arcs. The FFF mode has less scatter than the flattening filter mode. At the same time, it can greatly decrease patients' treatment time, reduce errors in respiratory movement and lower the probability of secondary malignancies [10]. In the process of providing breast cancer patients with VMAT treatment plans based on the FFF mode (FFF-VMAT), the main challenge was that with respiratory movements of the patients, especially in the case of breast swelling or deformation during radiation therapy course, the treatment plan may lack robustness. When patients with breast cancer undergo radiotherapy, respiratory movements raise the chest wall out to a certain distance. While margins of CTV are close to the body surface, planned target volume (PTV) cannot be extended to the outside of body surface [11]. In the use of Tangential Field Conformal Radiotherapy techniques, beams-eye-view (BEV) in a multiple leaf Collimator (MLC) position could be edited to extend the irradiation range of beams in this direction outwardly, so as to ensure that the dose near patient's epidermis could still meet clinical requirements. However, when using inverse optimization techniques such as VMAT for plan design, the MLC position could not be edited to realize the expansion of the radiation field beyond skin of the chest wall target area, and there will be certain risks of off-target effects. The usual solution is to add a certain thickness of Virtual Bolus (VB) on the skin surface of the target area, and to expand PTV to VB. The beam fields of the optimized radiation therapy plan could achieve a similar effect to expanding the tangent field's irradiation range. In final dose assessment, VB should be removed, and a dose calculation should be performed again. The main disadvantage of this method is that the dose distribution of radiotherapy plan used for the final evaluation is not optimized based on actual radiotherapy implementation status, so this plan is not guaranteed to be an actual optimal solution. Moreover, since VB is removed away, the final dose distribution is inadequate to protect OARs compared with the initial optimized results [12]. Using robust optimization in VMAT plan design of breast radiotherapy can also achieve more robust results than Tangential Field Conformal Radiotherapy and VB [13, 14]. When using FFF-VMAT technology combined with robust optimization method, it is necessary to carefully consider the impact of error caused by respiratory motion on the evaluation of planned dose because of the higher dose rate.

In this study, FFF-VMAT technology and robust optimization was used to develop a modified radical mastectomy radiotherapy plan for cancer of the left breast. The conventional setup error was still processed by the boundary expansion of CTV to PTV, and robust optimization was used to handle the extra uncertainty of chest wall caused by respiratory movement. In the case that the chest wall target area was shifted to a certain extent due to respiratory movement, by comparing the changes of target area coverage and organ dose at risk through the radiotherapy plan with or without robust optimization, we evaluated the role of robust optimization in FFF-VMAT radiotherapy treatment planning, so as to provide a reference for the postoperative treatment of cancer in the left breast.

Materials and methods

This retrospective study included 21 female patients admitted to Cancer Hospital Affiliated to the University of Chinese Academy of Sciences who underwent modified radical mastectomy from January 2019 to February 2020. In order to better demonstrate the advantages of robust optimization in respiratory movement, the subjects were selected who fit the following the criteria.

Inclusion criteria: Patients with thin chest wall target area and poor physical condition; Patients who were unable to undergo Deep inspiration breath-hold (DIBH) after modified radical surgery.

Exclusion criteria: Patients with good physical condition or feasible DIBH; Patients who underwent breast-conserving surgery.

In order to reduce the differences in the delineation of target areas and OARs, all patients were selected from the same chief physician. The median age of included patients was 56 years old (33-78). Patients were scanned with Phillips Brilliance large aperture Computed Tomography (CT) (Philips, BrillianceTM Big Bore CT, Netherlands) with 5-mm interval of reconstruction, and the scanning range was from the angle of Mandible to Navel. After scanning, the CT images were transmitted to a RayStation planning system. Then, the physician delineated target areas and OARs according to 2021 National Comprehensive Cancer Network (NCCN).

Target and normal tissue delineation

CTV and heart were delineated by a radiation oncologist. Meanwhile, the lungs, spinal cord and contralateral breast were sketched. CTV includes the left breast/chest wall and the supraclavicular and axillary level I-III nodes. All structures were delineated according to published international guidelines [15]. PTV was automatically generated and derived from CTV with 5 mm extension in the superior-inferior/anterior-posterior/left-right directions. An experienced clinician delineated targets and OARs based on the scanned transmitted CT images and clinical NCCN guidelines, including PTV that was CTV enlarged 5 mm in all direction; clinical target volume-chest (CTV-T): chest wall; clinical target volume-internal mammary (CTV-IMM): internal mammary area; planning target volume-chest (PTV-T): CTV-T enlarged 5 mm in all direction; planning target volume-internal mammary (PTV-IMM): CTV-IMM enlarged 5 mm in all direction; supraclavicular region (SC), including I, II, III; OARs included ipsilateral lung, right lung, heart, spinal cord. Completed clinical targets and OARs were then reviewed by the chief physician.

Plan design

All the radiotherapy plans were designed by the same physicist using RayStation planning system. 6 MV X-ray was selected for the plan, and the clinical prescription dose in planned target area was 50 Gy/25 fractions. To ensure radiation dose on the surface of breast skin, a 0.50 cm compensation bolus made of water-like-material was added to treatment planning and actual treatment process. Each patient took the same prescription dose at the same Ct and the same clinical target area to design two groups of FFF-VMAT plans with or without robust optimization with final dose scale to 95% of PTV volume covered by prescription dose (D_{95} was equal to prescription dose 5000 cGy of the planned target). In order to counteract possible outward movement of PTV-T caused by respiratory movement, the minimum dose volume histogram (DVH) objective function of PTV-T was set to “Robustness” when formulating robust optimization plan. Firstly, presenting the possible moving direction and range of clinical target area, in this case, “Robustness” option was set to Anterior 1.00 cm, Left 1.00 cm, and the other directions to 0 cm as default. Then the system will generate five optimization scenarios for comprehensive evaluation, traverse the value of the cost function in each scenario, and select the worst performed scenario as the next optimization benchmark, which were combined into the final optimization solutions. This method is called minimax optimization method [16, 17]. It has been verified that the optimization tool can also be used to develop photon radiotherapy plans [18, 19].

Plan analysis

First of all, comparative statistics of dosimetric parameters of the target and OARs were carried out for each patient’s plans, with or without robust optimization. Next, dose distribution generated from the original plan was carried out by simultaneously moving X and Y coordinates of the isocenter of original plan’s radiation field without changing other plan parameters so as to simulate outward movement of the target caused by respiratory movement. Dosimetric parameters of the target and OARs of two groups of plans, with or without robust optimization, were compared and evaluated.

Then, the data were collected for evaluation and analysis: (1) Evaluation of planned target area: it was required to meet the clinical prescription dose. Statistics were collected before and after shifting of planning target PTV D_{98},

Table 1. Dosimetry comparison of Target areas, OARs and Normal Tissue before displacement of central point of shooting field between no-robust and robust plans

Parameter	No-robust (cGy)	Robust (cGy)	*P*-value
PTV D98	4614.25±89.53	4624.96±109.9	0.611
PTV D95	4999.99±0.0002	5000.01±0.0003	0.320
PTV D50	5372.79±70.09	5347.49±42.46	0.078
PTV D2	5602.33±77.11	5570.53±45.94	0.045
CTV V50	0.99±0.004	1.00±0.003	0.196
PTV-T V50	94.95 (94.65~95.25)	96.04±0.75	0.000
CI (PTV)	0.85±0.03	0.84±0.04	0.030
HI (PTV)	0.18±0.02	0.1768±0.02172	0.213
Heart V40	0.026±0.02	0.02218±0.02015	0.003
Lung V30	0.0725±0.0124	0.06995±0.0138	0.003
Lung V20	0.0973±0.0154	0.0963±0.0181	0.315
Lung V5	0.2755±0.0462	0.2760±0.0464	0.798
Lung-L V30	0.1625±0.0279	0.1569±0.0310	0.004
Lung-L V20	0.2166±0.0330	0.2142±0.0386	0.256
Lung-L V5	0.4918±0.0540	0.4987±0.0601	0.091
Lung-R V5	0.1014±0.0564	0.0968±0.0496	0.227
Lung D	700.14±85.984	697.18±91.717	0.385
Lung-L D	1273.668±134.635	1265.827±157.045	0.353
Lung-R D	238.9906±68.631	239.91±64.6686	0.850
Heart D	654.234±162.474	645.861±164.988	0.142
Spinal cord	1516.6698±558.437	1315.8838±696.236	0.002
nt	294.1508±33.3821	308.4764±33.7037	0.001

Note: OARs: organs at risk, PTV: planned target volume, CTV: clinical target volume, CI: conformity index, HI: homogeneity index, Lung-L: Left Lung, Lung-R: Right Lung, V: Vloume, D: dose.

D_{95}, D_2 (D_x represented dose of x%PTV volume irradiated), conformity index (CI) and homogeneity index (HI). Among them, CI = (PTV_{ref}/V_{PTV})/(PTV_{ref}/V_{ref}), PTV_{ref} is the prescription dose of PTV; V_{PTV} is volume of PTV; V_{ref} is volume of prescription dose accepted by whole body (V_x represents percentage of target volume containing xGy, and D_{max} represents maximum dose of target). CI value is between 0 and 1. The closer the CI value to 1, the better the conformality of dose distribution to the target area. HI = (D_2 - D_{98})/D_{50}, and HI value is between 0 and 1. The closer the HI value to 0, the better the uniformity of dose distribution. (2) Dosimetric parameters of OARs: before and after shifting, V_{30}, V_{20}, V_5 Mean Dose (D_{mean}) of ipsilateral lung and whole lung, V_5 and D_{mean} of right lung, Heart's V_{40} and D_{mean}, $V_{0.1}$ (cm^3) (V_x (cm^3) of brachial plexus represents the maximum dose in xcm^3 volume) and $V_{0.3}$ (cm^3) dose of anterior descending coronary artery were collected.

Statistical methods

The data obtained were statistically analyzed by SPSS 23.0 software. The results of FFF-VMAT plan with or without robust optimization were tested for a normal distribution. Then, the data conforming to a normal distribution were tested by paired t-test or nonparametric test. The quantitative parameters were expressed as mean ± variance or median (the results retain 2 decimal places). The two significant digits after the decimal point were retained (P<0.05 was considered to be a statistical difference).

Results

Comparison of target dose parameters

Before getting shifted, the CI of PTV with robust optimization were lower than those without robust optimization (P<0.05). PTV-T V50 with robust optimization was slightly better than that without robust optimization (P<0.001). See **Table 1**. There were no statistical differences in other target-related parameters. Although there were slight differences in some dosimetric parameters between the two groups, they all met requirements of clinicians.

In order to simulate movement of the chest wall caused by respiratory movement, the dose distribution with or without robust optimization plan was calculated and evaluated after the field center was shifted to 0.50 cm. The D_{98}, D_{95}, D_2 and CI of PTV with robust optimization were higher than those without robust optimization (P<0.05). HI of PTV with robust optimization was lower than that without robust optimization (P<0.05). See **Table 2**. The V_{50} of PTV-T with robust optimization was higher than that without robust optimization (P<0.05). CTV with robust optimization was higher than that without robust optimization (P<0.001). See **Figure 1**. The difference of CTV coverage before and after robust optimization or without robust optimization could be found. The blade width of planned multi-leaf collimator with robust opti-

Table 2. Comparison of dose of Target areas, OARs and Normal Tissue after displacement of central point of shooting field between no-robust and robust plans

Parameter	No-robust	Robust	*P*-value
PTV D98	4291.7780±196.9615	4696.8682±80.8172	0.000
PTV D95	4593.4782±158.5439	4885.9148±36.6903	0.000
PTV D50	5188.2312±73.0069	5210.0772±45.5303	0.125
PTV D2	5514.1125±93.0708	5580.43 (5526.89~5635.68)	0.001
CTV V50	0.7912±0.0951	0.9058±0.0443	0.000
PTV-T V50	0.7728±0.0894	0.8933 (0.8519~0.9210)	0.000
CI (PTV)	0.6491±0.1186	0.6928±0.0796	0.001
HI (PTV)	0.2356±0.0415	0.1722 (0.15~0.18)	0.000
Heart V40	0.0606±0.0353	0.0622±0.0401	0.794
Lung V30	0.1080±0.0151	0.1050 (0.979~0.1212)	0.140
Lung V20	0.1349±0.0187	0.1346±0.0211	0.795
Lung V5	0.3278±0.0501	0.3333±0.0483	0.059
Lung-L V30	0.2410±0.0321	0.2396±0.0357	0.630
Lung-L V20	0.2939±0.0346	0.2939 (0.2703~0.3280)	0.741
Lung-L V5	0.5550±0.0509	0.5660±0.0555	0.006
Lung-R V5	0.1392±0.0700	0.1462±0.0565	0.353
Lung D	898.541±102.4286	901.598±107.1063	0.363
Lung-L D	1648.813±155.8893	1649.3589±179.3673	0.945
Lung-R D	294.6492±83.6333	299.6784±78.3141	0.369
Heart D	903.7943±222.5719	895.5513±227.5937	0.200
Spinal cord	2031.4301±763.9234	1763.5515±963.9730	0.000
nt	342.2973±36.6788	358.9020±37.0551	0.000

Note: OARs: organs at risk, PTV: planned target volume, CTV: clinical target volume, CI: conformity index, HI: homogeneity index.

mization was about 0.81 cm larger than that without robust optimization (**Figure 2**), which compensates the target dose in case of respiratory moments.

Comparison of OARs dose parameters

Before displacement, the ipsilateral lung's V_{30}, whole lung's V_{30}, heart's D_{mean}, heart's V_{40}, spinal cord of the treatment plan with robust optimization were significantly lower than those without robust optimization (P<0.05). However, there was no statistical difference in other parameters (**Table 1**).

After transposition, the V_5 of lung without robust optimization was significantly lower than that of the treatment plan with robust optimization. The D_{max} of spinal cord of the treatment plan with robust optimization was significantly lower than that without robust optimization (P<0.05). There were no statistical differences in other dose parameters. After evaluation, dosing which would endanger the organs was within the clinical requirements (**Table 1**).

Discussion

In this study, we aimed to solve the problem of insufficient clinical target dosing due to respiratory motion during radiotherapy for postoperative cancer of the left breast. Robust optimization was introduced to limit the minimum dose of PTV-T in patient's planned target area. After shifting, we found that the robust optimization plans provided better target coverage, HI, $PTVD_{98}$, D_{95} and D_2 than in plans without robust optimization (P< 0.05). The dose distribution in the robust optimization plans was less affected by perturbations. The PTV-T with robust optimization were slightly better than that without robust optimization (P<0.001). The target coverage rate of CTV V_{50} without robust optimization was 79.12±9.51%, and the target coverage rate with robust optimization was 90.58±4.42%. There was a significant difference in the target coverage of CTV V_{50} between the two treatment plans (P<0.001). It can be clearly seen from **Figure 1** that a shifted isocenter of the beam field leads to changes in CTV coverage.

In terms of OARs, there were statistical differences in V_5 of patients' ipsilateral lung and D_{max} of spinal cord. The V_5 of treatment plan without robust optimization in patients' ipsilateral lung was lower than that with robust optimization, and the D_{max} of the spinal cord was significantly higher without robust optimization than that with robust optimization. In terms of machine execution efficiency, there was no statistical difference between the total beam on time and total monitor units (MUs).

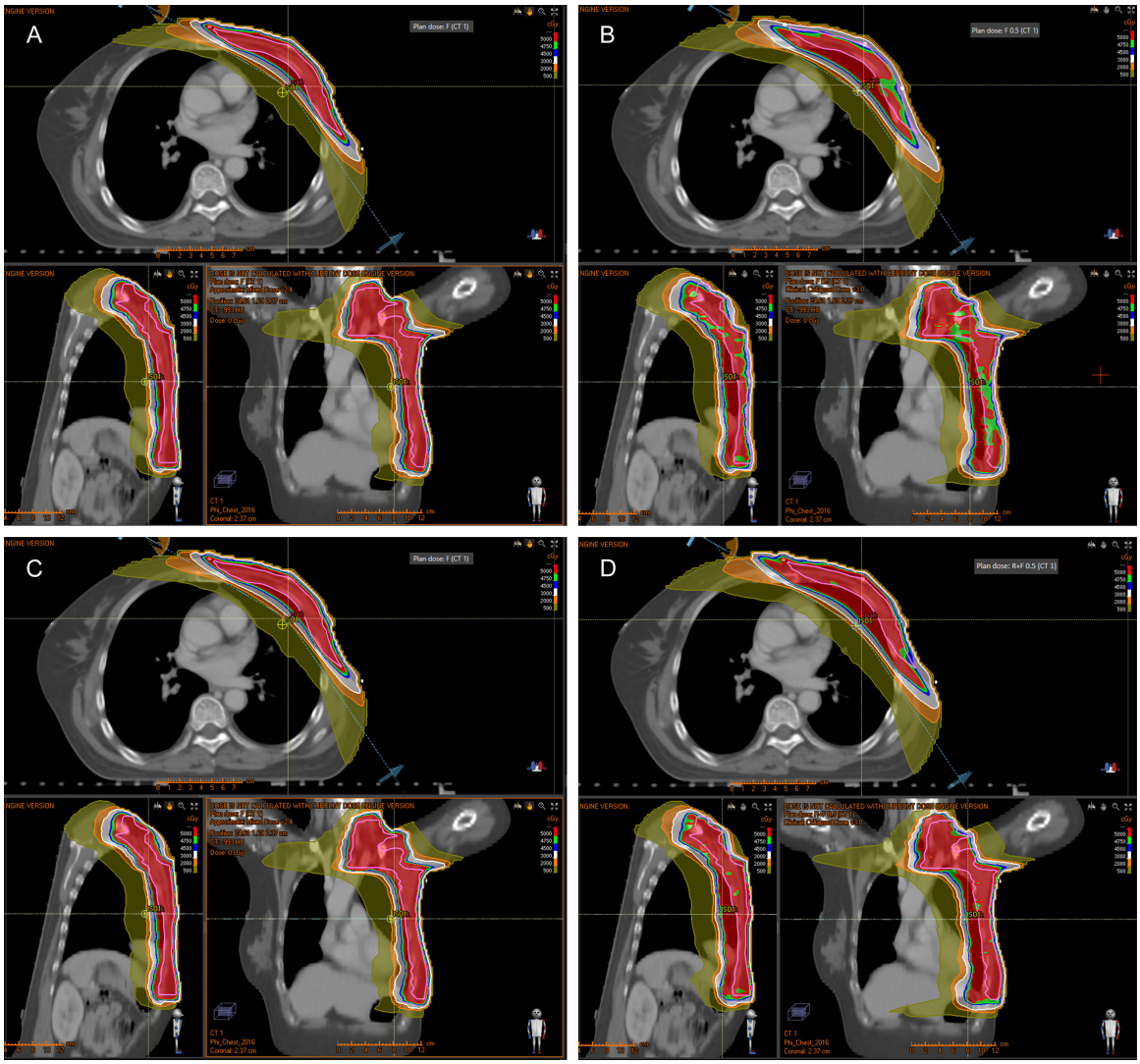

Figure 1. Dose distribution before and after displacement of central field in beams-eye-view. A: No-robust optimization plan before shifting; B: No-robust optimization plan after shifting; C: Robust optimization plan before shifting; D: Robust optimization plan after shifting.

In order to reduce the errors caused by patients' respiratory movement in actual treatment, robust optimization was added to the radiotherapy plan. Clinical studies have shown that it not only improved the coverage rate of the clinical target area, but also reduced the dose of OARs. The experiments done by Mahmoudzadeh team's proved that the introduction of robust optimization could potentially reduce the need for deep inspiration breath-hold technology, allowing patients to have reduced dose exposure to the heart with free breath, and improve the dose coverage at the tumor area [20]. Fredriksson proposed that adding robust optimization could significantly increase the patient's skin dose, and to some extent, it could replace the efficacy of VB [21]. Dunlop's team added robust optimization to study breast cancer radiotherapy based on organ motion, and found that the D_{98}, D_{95}, D_{50} and D_{2} of that CTV that added robust optimization were significantly different from those without robust optimization [13]. They also proposed that the use of robust optimization based on organ motion to generate a VMAT plan was clinically acceptable for the typical and extreme target area changes during treatment [13]. Hideharu Miura's team verified the advantages of introducing robust optimization in other tumor types with greater CTV activity, such as Larynx can-

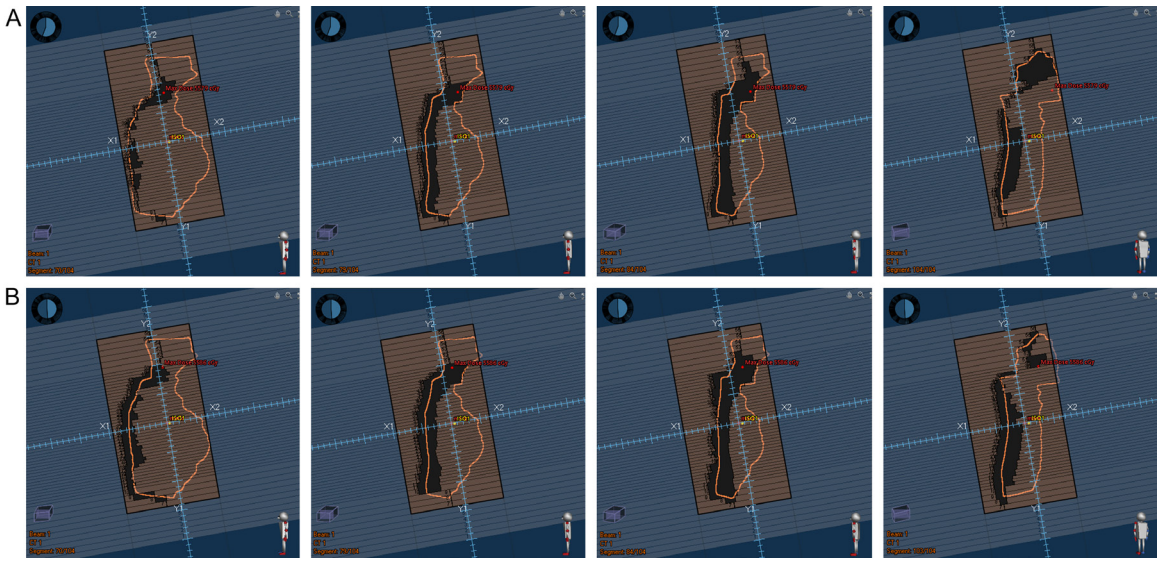

Figure 2. Comparison of state of multi-leaf collimator. A: MLC aperture of field direction without robust optimization. B: MLC aperture of field direction with robust optimization (from left to right, accelerator angle is 76°, 96°, 118°, 148° in the state of multi-leaf collimator, robust optimization plan was better than no robust optimization, and blade of multi-leaf collimator has expanded about 0.81 cm). MLC: multiple leaf Collimator.

cer, and they found that robust-optimized plan had better CTV coverage rate and less carotid artery exposure dose than those without robust optimization [22]. This is slightly different from the actual exposure dose of OARs dose parameters in this study. The exposure dose of the ipsilateral lung V5 with robust optimization was higher than that without, because the improved CTV coverage in our study was at the expense of a low dose bath to healthy tissue, thereby delivering a higher volume of low dose to the ipsilateral lungs than that in plans without robust optimization.

The introduction of PTV was aimed at reducing the error impact of a series of radiotherapy procedures on CTV. The clinical target area of postoperative patients with cancer of the left breast is long and narrow, and close to the surface of skin, while CTV can only expand to the chest cavity, not to the outer surface of skin. Compared with other tumor target areas, respiratory movement is more likely to affect the actual radiation dose of breast cancer's CTV. Introduction of robust optimization significantly improved this situation. As seen in **Table 1**, the edges of multi-blade collimator apertures in BEV with robust optimization plan were spared by about 0.81 cm, compared with that without robust optimization. When the center of beam field moved a same distance, the coverage rate of CTV V_{50} dose in robust optimized treatment plan increased by about 14.49%, while V_5 of the ipsilateral lung only increased by about 1.00%. The possible reason for the increase was the introduction of robust optimization, which optimized the movement of target area to the left and front directions in case of respiratory movement. When seeking the best solution under the condition of increasing uncertain factors, the actual volume of the illuminated target area increases and the scattering amount increases in the same proportion. Although robust optimization could ensure the dose coverage of target area to a certain extent, it was still recommended to re-check the patient's position or to use deep inspiration breath-hold techniques as appropriate if patient's respiratory movement amplitude caused the difference between outer contour of target area and the planned target area exceeds 0.50 cm during Cone Beam Computed Tomography (CBCT) verification before the delivery of treatment plan.

In summary, under the premise that with or without robust optimization we met the clinical requirements before displacement, the deviation of CTV target area of human respiratory motion was simulated by changing the position of the center point of the radiation field. VMAT plans using the robustness feature of Ray-

Station are less affected on average than that without robust optimization. Furthermore, it could be seen that after the shift, the robust-optimized treatment plan was better for the D_{98}, D_{95}, D_2, CI, HI of PTV and the most active PTV-T dose parameters. CTV coverage rate in the robust-optimized plan was significantly higher than that without, and better CTV prescription dose coverage usually means more effective tumor control. Therefore, a FFF-VMAT robust-optimized treatment plan is better than a plan without robust optimization.

The limitation of this study is that the robust optimization is only carried out for the target region, and the protection of OARs is not taken into extra consideration. As a result, the dose level of OARs increases in the case of respiratory movement. In addition, by changing the center point of the beam field to simulate breathing movement, only the target movement caused by respiratory movement can be simulated, which is not accurate in OARs movement. In the following studies, we will consider scanning with 4-Dimensional CT, to use CT of different respiratory phases for dose assessment, and use a new CT that simulates motion generated by elastic deformation of the original CT for dose assessment, or to use bionic models and detectors that can simulate respiratory motion for dose measurement instead of simple central point displacement of the radiation field. If more robust optimization is needed to improve the follow-up radiotherapy effect and the evidence for clinical use, the sample size can be increased for research.

Conclusions

Robust optimization can be adopted in the development of a postoperative radiotherapy plan for cancer of the left breast, for it ensures that the target dose coverage and the dose limit of organs-at-risk still meet the clinical requirements under conditions of chest wall displacement caused by respiratory movement.

Acknowledgements

This study was supported by grants from Health Department of Zhejiang Province (2018ZD014, 2019C03003 2020KY472, and 2021KY571). This study was approved by the Zhejiang Cancer Hospital Ethics Committee (IRB-2021040).

Disclosure of conflict of interest

None.

Address correspondence to: Shengye Wang, Department of Radiation Physics, The Cancer Hospital of The University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou 310022, Zhejiang, China. E-mail: wangsy@zjcc.org.cn; Jianliang Zhou, University of South China, School of Nuclear Science and Technology, Hengyang 421001, Hunan, China. E-mail: 13327341099@189.cn

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.

[2] Thorsen LB, Offersen BV, Danø H, Berg M, Jensen I, Pedersen AN, Zimmermann SJ, Brodersen HJ, Overgaard M and Overgaard J. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol 2016; 34: 314-320.

[3] Lin Y and Wang B. Dosimetric absorption of intensity-modulated radiotherapy compared with conventional radiotherapy in breast-conserving surgery. Oncol Lett 2014; 9: 9-14.

[4] Dogan N, Cuttino L, Lloyd R, Bump EA and Arthur DW. Optimized dose coverage of regional lymph nodes in breast cancer: the role of intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2007; 68: 1238-1250.

[5] Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, Peckitt C, Reise S, Ross G, Sharp G, Symonds-Tayler R, Tait D and Yarnold J. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 2007; 82: 254-264.

[6] Pignol JP, Olivotto I, Rakovitch E, Gardner S, Sixel K, Beckham W, Vu TT, Truong P, Ackerman I and Paszat L. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 2008; 26: 2085-2092.

[7] Virén T, Heikkilä J, Myllyoja K, Koskela K, Lahtinen T and Seppälä J. Tangential volumetric modulated arc therapy technique for left-sided breast cancer radiotherapy. Radiat Oncol 2015; 8: 10-79.

[8] Chen YZ, Li J, Liao XF, Li CR, Sung CT, Kang SW and Wang P. Dosimetric comparison between VMAT and IMRT for postoperative radiotherapy of breast carcinoma. J Cancer Control Treat 2014; 27: 226-230.
[9] Ranger A, Dunlop A, Hutchinson K, Convery H, Maclennan MK, Chantler H, Twyman N, Rose C, McQuaid D, Amos RA, Griffin C, deSouza NM, Donovan E, Harris E, Coles CE and Kirby A. A dosimetric comparison of breast radiotherapy techniques to treat locoregional lymph nodes including the internal mammary chain. Clin Oncol (R Coll Radiol) 2018; 30: 346-353.
[10] Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys 2006; 65: 1-7.
[11] Ma C, Chen M, Long T, Parsons D, Gu X, Jiang S, Hou Q and Lu W. Flattening filter free in intensity-modulated radiotherapy (IMRT) - Theoretical modeling with delivery efficiency analysis. Med Phys 2019; 46: 34-44.
[12] Sankar A and Velmurugan J. Different intensity extension methods and their impact on entrance dose in breast radiotherapy: a study. J Med Phys 2009; 34: 200-205.
[13] Dunlop A, Colgan R, Kirby A, Ranger A and Blasiak-Wal I. Evaluation of organ motion-based robust optimisation for VMAT planning for breast and internal mammary chain radiotherapy. Clin Transl Radiat Oncol 2019; 16: 60-66.
[14] Fredriksson A, Forsgren A and Hårdemark B. Minimax optimization for handling range and setup uncertainties in proton therapy. Radiother Oncol 2012; 104: 45-51.
[15] Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, Blair SL, Burstein HJ, Dang C, Elias AD, Giordano SH, Goetz MP, Goldstein LJ, Hurvitz SA, Isakoff SJ, Jankowitz RC, Javid SH, Krishnamurthy J, Leitch M, Lyons J, Matro J, Mayer IA, Mortimer J, O'Regan RM, Patel SA, Pierce LJ, Rugo HS, Sitapati A, Smith KL, Smith ML, Soliman H, Stringer-Reasor EM, Telli ML, Ward JH, Wisinski KB, Young JS, Burns JL and Kumar R. NCCN guidelines® insights: breast cancer, version 4.2021. J Natl Compr Canc Netw 2021; 19: 484-493.
[16] Liu W, Zhang X, Li Y and Mohan R. Robust optimization of intensity modulated proton therapy. Med Phys 2012; 39: 1079-1091.
[17] Stuschke M, Kaiser A, Pöttgen C, Lübcke W and Farr J. Potentials of robust intensity modulated scanning proton plans for locally advanced lung cancer in comparison to intensity modulated photon plans. Radiother Oncol 2012; 104: 45-51.
[18] Stuschke M, Kaiser A, Abu Jawad J, Pöttgen C, Levegrün S and Farr J. Multi-scenario based robust intensity-modulated proton therapy (IMPT) plans can account for set-up errors more effectively in terms of normal tissue sparing than planning target volume (PTV) based intensity-modulated photon plans in the head and neck region. Radiat Oncol 2013; 8: 1-5.
[19] Nguyen D, Corbet C, Largeron G, Josserand-Pietri F, Yossi S and Khodri M. Is robust optimization better than virtual bolus method to achieve skin flash in breast VMAT plans? Radiother Oncol 2018; 127: S1027-S1027.
[20] Mahmoudzadeh H, Lee J, Chan TC and Purdie TG. Robust optimization methods for cardiac sparing in tangential breast IMRT. Med Phys 2015; 42: 2212-2222.
[21] Fredriksson A and Hårdemark B. EP-1503 skin flash of breast in IMRT and VMAT using robust optimization. Radiother Oncol 2012; 103: S575-S576.
[22] Miura H, Doi Y, Ozawa S, Nakao M, Ohnishi K, Kenjo M and Nagata Y. Volumetric modulated arc therapy with robust optimization for larynx cancer. Phys Med 2019; 58: 54-58.