ACTA ONCOLOGICA, 2017
VOL. 56, NO. 11, 1428–1436
https://doi.org/10.1080/0284186X.2017.1348625

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

The influence of breathing motion and a variable relative biological effectiveness in proton therapy of left-sided breast cancer

Jakob Ödén[a,b], Iuliana Toma-Dasu[a,c], Kjell Eriksson[b], Anna Maria Flejmer[d] and Alexandru Dasu[e,f]

[a]Department of Physics, Medical Radiation Physics, Stockholm University, Stockholm, Sweden; [b]RaySearch Laboratories, Stockholm, Sweden; [c]Department of Oncology and Pathology, Medical Radiation Physics, Karolinska Institutet, Stockholm, Sweden; [d]Department of Oncology and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden; [e]The Skandion Clinic, Uppsala, Sweden; [f]Department of Medical and Health Sciences, Linköping University, Linköping, Sweden

ABSTRACT

Background: Proton breast radiotherapy has been suggested to improve target coverage as well as reduce cardiopulmonary and integral dose compared with photon therapy. This study aims to assess this potential when accounting for breathing motion and a variable relative biological effectiveness (RBE).

Methods: Photon and robustly optimized proton plans were generated to deliver 50 Gy (RBE) in 25 fractions (RBE = 1.1) to the CTV (whole left breast) for 12 patients. The plan evaluation was performed using the constant RBE and a variable RBE model. Robustness against breathing motion, setup, range and RBE uncertainties was analyzed using CT data obtained at free-breathing, breath-hold-at-inhalation and breath-hold-at-exhalation.

Results: All photon and proton plans (RBE = 1.1) met the clinical goals. The variable RBE model predicted an average RBE of 1.18 for the CTVs (range 1.14–1.21) and even higher RBEs in organs at risk (OARs). However, the dosimetric impact of this latter aspect was minor due to low OAR doses. The normal tissue complication probability (NTCP) for the lungs was low for all patients (<1%), and similar for photons and protons. The proton plans were generally considered robust for all patients. However, in the most extreme scenarios, the lowest dose received by 98% of the CTV dropped from 96 to 99% of the prescribed dose to around 92–94% for both protons and photons. Including RBE uncertainties in the robustness analysis resulted in substantially higher worst-case OAR doses.

Conclusions: Breathing motion seems to have a minor effect on the plan quality for breast cancer. The variable RBE might impact the potential benefit of protons, but could probably be neglected in most cases where the physical OAR doses are low. However, to be able to identify outlier cases at risk for high OAR doses, the biological evaluation of proton plans taking into account the variable RBE is recommended.

ARTICLE HISTORY
Received 1 May 2017
Accepted 21 June 2017

Introduction

As new proton therapy centers are emerging continuously worldwide, the capacity of treating patients with protons is rapidly increasing. Since the target conformity and capability of sparing organs at risk (OAR) have improved for photon therapy over the last decade, the focus for selecting patients suitable for proton therapy has switched slightly, from primarily evaluating the target coverage to its ability to reduce side effects while maintaining sufficient tumor control probability (TCP). Such an approach could be formulated as a normal tissue complication probability (NTCP) based selection system, where a proton plan must demonstrate a substantially lower NTCP for at least one primary OAR [1]. However, such a NTCP comparison is typically performed assuming a constant relative biological effectiveness (RBE) of 1.1 for protons, although the RBE dependence on, e.g., biological endpoint, dose, linear energy transfer (LET) and cell type is well established *in vitro* [2]. The evidence for how the RBE varies *in vivo* is on the other hand lacking, but detailed studies have confirmed the presence of these effects even *in vivo* [3]. Moreover, the uncertainties due to setup, range, breathing motion and biological effects could also be included as part of the selection process of protons. These uncertainties could potentially be included already in a robust optimization, a technique which so far has focused on the physical uncertainties [4], but the assessment of their impact is perhaps more suitable to include in the plan evaluation.

Several studies have evaluated the potential influence of a variable proton RBE through plan comparisons with photon therapy [5–7]. The main conclusions made have been that, although the variable RBE generally do not jeopardize the often substantially lower integral dose of protons compared to photons, it might slightly compromise the target dose for high α/β targets (e.g., CNS and H&N tumors) and also

CONTACT Jakob Ödén jakob.oden@fysik.su.se Department of Physics, Medical Radiation Physics, Stockholm University, Karolinska University Hospital, P9:02, SE-171 76 Stockholm, Sweden

Supplemental data for this article can be accessed here.

increase the predicted NTCP for most OARs [6–8]. On the other hand, for low α/β targets (e.g., breast and prostate), the target dose is generally predicted to be higher than using the constant RBE of 1.1 [5,7,8]. However, all these effects are strongly affected by the fractionation schedule, α/β assumptions, RBE model, etc. and should be used conservatively, especially since the inclusion of such parameters introduces additional uncertainties in the final RBE-weighted dose for all tissues [8].

Although several proton and photon comparative planning studies have indicated the advantages of proton therapy for breast cancer treatment [9–12], no study has incorporated the variable RBE in the plan comparison to our knowledge. As breast cancer patients constitute a large patient group, which undoubtedly benefit from radiotherapy in terms of local control and overall survival [13], such inclusion might be of importance for the selection of breast patients for proton therapy. Moreover, as it exists a concern of cardiopulmonary toxicity in long-term survivors [14], the potential effect of the variable RBE should be investigated.

Hence, this study aims to evaluate the impact on the plan quality of including the variable RBE in the proton and photon plan comparison for free-breathing (FB) left-sided whole breast cancer patients.

Methods

Patients, volumes and CT datasets

Twelve thoracic patients with CT scans in a body immobilization system with abdominal compression were included in this study. All patients demonstrated regular breathing patterns and had the breast tissue clearly visible for contouring in the three CT scans acquired; FB, breath-hold-at-inhalation (BHI) and breath-hold-at-exhalation (BHE). The CT scans were obtained in supine position with 2 mm slice thickness. The clinical target volume (CTV), planning target volume (PTV), both lungs, heart, the left anterior descending artery (LAD) and the contralateral breast were defined on all CT sets according to the RTOG guidelines. The CTV included the whole left breast and the PTV (only used for photons) was defined as a uniform expansion of the CTV with 5 mm. Both target volumes were cropped 5 mm below the skin surfaces. The structures were independently delineated on each CT dataset by one experienced radiation oncologist using suitable window settings and the structure sets belonging to the same patient were visually checked for consistency.

Deformable image registration

Deformable image registrations (DIRs) were performed in a research version of RayStation v4.6 (RaySearch Laboratories, Stockholm, Sweden) for all patients using the anatomically constrained deformation algorithm (ANACONDA) [15]. ANACONDA is an image intensity-based hybrid algorithm which takes both intensity- and geometrically-based similarity measures into account when solving the non-linear optimization problem formulated to calculate the deformation vector field on the deformation grid. For dose mapping, DIRs were performed between the FB CT and the two extreme phases (BHI and BHE). For target motion evaluation, the DIR was performed between the BHI and BHE.

Treatment planning

Photon and proton plans were generated on the FB CT scan for all 12 patients using the research version of RayStation. The clinical dose was calculated as dose-to-water using the collapsed cone dose engine for photons and the pencil beam dose engine for protons with voxel volumes of $3 \times 3 \times 3\,mm^3$. The prescribed dose (PD) was 50 Gy (RBE) in 25 fractions using RBE = 1.1 for protons and was normalized to be equal to the median dose ($D_{50\%}$) of the CTV for all plans. The photon plans were created using a hybrid IMRT technique, consisting of two open tangential fields (approximately 300° and 130°) delivering approximately 60% of the target dose and two IMRT fields in the same gantry angles delivering the remaining 40% of the target dose. Similar hybrid photon techniques have been presented previously [16]. The proton plans were robustly optimized intensity modulated proton therapy (IMPT) plans utilizing the minimax optimization in RayStation [4] with three oblique fields (approximately 340°, 20° and 60°). The robustness parameters used for the CTV coverage were 5 mm uniformly for the setup uncertainty and ±3% for the range uncertainty. Proton energies of 70–230 MeV were available and hence a range shifter with a water equivalent thickness of 4 cm was used for all fields to ensure superficial target coverage. This field arrangement is similar to other proton breast therapy studies [11,12]. Additionally to RBE = 1.1, the RBE-weighted dose was also calculated using the variable RBE model by Wedenberg et al. [17]. To do so, the dose-average LET (LET_d) was calculated on voxel level using an already existing Monte Carlo dose framework for proton transport inside RayStation [6,7] and α/β values were assigned on voxel level. An α/β of 3.5 Gy was used for the CTV [18], 4 Gy for the lungs [19] and a conservative value of 3 Gy for the remaining normal tissues [20]. The RBE calculations were performed voxel-wise using IronPython through the scripting tool in RayStation.

Robustness calculations

For each nominal plan, the robustness against setup and range uncertainties (only setup for the hybrid IMRT plans) was calculated for each CT phase separately and in combination with a simulated breathing motion. Both the generic RBE of 1.1 and the variable RBE model by Wedenberg were considered for the IMPT plans. The worst-case lower and upper dose boundary per voxel was determined using a previously described method [8], from which cumulative lower and upper DVHs were generated for all ROIs. Beyond the setup and range uncertainties, the fractionation effect [21] and the uncertainties in the α/β, LET_d and the model parameter were included when the Wedenberg RBE model was used. These uncertainties were accounted for through a Monte Carlo sampling technique from probability density functions (PDFs) of the model input parameters (LET_d, α/β

and the model fitting parameter). The normally distributed PDF for the LET_d was created using a 95% confidence interval (CI) of ±10% of the nominal LET_d for each voxel and range scenario evaluated (0% or ±3%). The normally distributed PDFs for the α/β were created using 3.5 Gy (95% CI: 1.0–6.0 Gy) for the CTV, 4.0 Gy (95% CI: 2.0–6.0 Gy) for the lungs and 3.0 Gy (95% CI: 1.5–4.5 Gy) for the remaining normal tissues, whereas the PDF for the model input parameter was a log-normal distribution fitted to the 95% CI stated in the original paper [17]. All these PDFs were equal to the ones used in the original paper describing the robustness evaluation method [8].

Setup and range uncertainties

The dose distributions considering setup and range uncertainties were recalculated on each of the three CT scans separately to simulate extreme scenarios where the whole treatment was delivered in a single breathing phase. The CT density was altered ±3% for the IMPT plans and the isocenter of the nominal IMPT and hybrid IMRT plans was isotropically shifted 5 mm in 14 directions, six shifts along the positive and negative directions along the principal axes and eight shifts along the diagonal axes for all triplets possible. Thus, a total of 45 scenarios (including 0% and ±3% range error with no shifting) were created for each CT for the IMPT plans and 15 scenarios per CT for the hybrid IMRT plans, from which lower and upper worst-case doses were generated independently for each voxel in accordance with the previous method description [8].

Breathing motion combined with setup and range uncertainties

To incorporate breathing motion into the evaluation, the doses from each of the 45 calculated error scenarios for the IMPT plans (15 for the hybrid IMRT plans) described above were mapped onto the reference FB CT scan using the DIRs and accumulated with equal dose weighting for each of the three breathing phases. This approach simulated a treatment delivery in FB assuming that the breathing consisted of three CT phases (BHI, FB and BHE) with equal likelihood. This resulted in 45 or 15 dose scenarios accumulated on the FB CT scan per patient, where one was the special case of only breathing motion and no setup or range error. Lower and upper worst-case doses for the combination of breathing motion with setup and range uncertainties were then generated independently for each voxel in accordance with the previous method description [8].

Evaluation of target motion and volume change

To assure that the BHI and BHE CT scans corresponded to realistic breathing motion amplitudes for FB, the center of mass movement of the CTV between the scans was derived. This was done in two separate ways, the center of mass difference between the CTVs on the BHI and BHE CT, and the center of mass difference between the CTV on the BHE and the CTV mapped from the BHI CT to the BHE CT using the corresponding DIR. The difference in volume of the CTV was also evaluated for the two procedures.

Nominal plan evaluation

The CTV coverage was quantified using the metrics D_{mean}, $D_{98\%}$, $D_{2\%}$, $V_{95\%}$, $V_{105\%}$ and the homogeneity index (HI). The HI was defined as $HI = \frac{D_{2\%} - D_{98\%}}{D_{mean}}$, where D_{mean} is the mean dose, $D_{2\%}$ and $D_{98\%}$ are the least doses received by 2% and 98% of the CTV, respectively. $V_{95\%}$ and $V_{105\%}$ are the volumes of the CTV receiving at least 95% and 105% of the PD, respectively. The clinical goals for the CTV (and photon PTV) were defined as, $D_{98\%} \geq 95\%$ of the PD and $D_{2\%} \leq 105\%$ of the PD. D_{mean}, $D_{2\%}$ and the volume covered by 5 and 25 Gy (RBE) ($V_{5Gy\ (RBE)}$ and $V_{25Gy\ (RBE)}$) were calculated for the heart, D_{mean} and $D_{2\%}$ for the LAD, D_{mean}, $D_{2\%}$, $V_{5Gy\ (RBE)}$, $V_{10Gy\ (RBE)}$ and $V_{20Gy\ (RBE)}$ for the left lung. Additionally, the NTCP for Grade ≥2 radiation pneumonitis in the lungs [22] and the integral dose to the normal tissues were calculated for each patient. The integral dose was calculated from average doses and volumes of the delineated structures using volumetric mass densities of 0.26 g/cm^3 for the lungs and 1.06 g/cm^3 for other tissues [11]. The normal tissue doses were always tried to be kept to a minimum after ensuring fulfillment of the target goals, with clinical goals of $D_{mean} \leq 2$ Gy (RBE) for the heart, $D_{mean} \leq 5$ Gy (RBE) for the left lung and NTCP ≤ 1% for the lungs. Due to very limited clinical data, no specific clinical goal was used for the LAD.

Differences between dosimetric metrics obtained by photon and proton plans were tested for statistical significance using the paired, two-tailed non-parametric Wilcoxon's signed-rank test. This test was chosen since the differences may not be normally distributed. Both the constant RBE of 1.1 and the Wedenberg RBE model were considered for the proton plans.

Robustness evaluation

Lower and upper worst-case DVHs were generated for all ROIs and robustness scenarios by using the independently calculated lower and upper worst-case doses for each voxel. The robustness criteria for CTV coverage was set to the nominal clinical goals, $D_{98\%} \geq 95\%$ of the PD for the lower worst-case DVH and $D_{2\%} \leq 105\%$ of the PD for the upper worst-case DVH. The normal tissue robustness criteria for the worst-case scenarios were stretched slightly compared to the nominal goals to $D_{mean} \leq 5$ Gy (RBE) for the heart and $D_{mean} \leq 10$ Gy (RBE) for left lung, while the criteria for lung NTCP ≤ 1% were maintained.

Results

Target motion and volume change

The 3D vector of the center of mass movement of the CTV was 5.1 ± 3.7 mm (range 0.5–12.5 mm), when derived using the CTV mapping. When comparing the mass center of the

Table 1. Mean values and one standard deviation for dosimetric parameters for all 12 patients. The variable RBE model used is the one by Wedenberg et al. [17], assuming an α/β of 3.5 Gy for the CTV, 4.0 Gy for the lungs, 3.0 Gy for the heart and LAD.

	Photons Mean (SD)	Protons $RBE_{1.1}$ Mean (SD)	Protons $RBE_{Variable}$ Mean (SD)	p-Value[b] $RBE_{1.1}$ vs. photons	p-Value[b] $RBE_{Variable}$ vs. photons
CTV					
D_{mean} [Gy (RBE)]	50.0 (0.0)	50.0 (0.0)	53.5 (0.9)	.02	≪.05
$D_{98\%}$ [Gy (RBE)]	48.8 (0.2)	49.3 (0.1)	51.7 (0.9)	≪.05	≪.05
$D_{2\%}$ [Gy (RBE)]	51.2 (0.3)	51.0 (0.2)	56.1 (0.8)	.11	≪.05
HI (%)	4.7 (1.0)	3.4 (0.6)	8.2 (0.8)	≪.05	≪.05
Heart					
D_{mean} [Gy (RBE)]	0.8 (0.4)	0.1 (0.1)	0.2 (0.1)	≪.05	≪.05
$D_{2\%}$ [Gy (RBE)]	3.6 (3.6)	1.0 (1.0)	1.9 (1.8)	≪.05	.01
LAD					
D_{mean} [Gy (RBE)]	5.5 (4.8)	1.6 (1.1)	2.9 (1.9)	≪.05	.01
$D_{2\%}$ [Gy (RBE)]	12.6 (11.4)	3.7 (2.6)	6.5 (4.3)	≪.05	.01
Left lung					
D_{mean} [Gy (RBE)]	3.1 (0.9)	1.3 (0.3)	2.2 (0.4)	≪.05	≪.05
$V_{20Gy\ (RBE)}$ (%)	5.1 (2.4)	1.4 (0.6)	3.4 (1.0)	≪.05	.03
NTCP[a] (%)	0.5 (0.04)	0.4 (0.01)	0.4 (0.02)	≪.05	≪.05
Integral dose [Gy (RBE) kg]	36.9 (12.5)	28.3 (8.1)	35.2 (9.5)	≪.05	≫.05

[a]Grade ≥2 radiation pneumonitis using the LKB model ($n = 1$, $m = 0.37$, TD50 = 30.8 Gy) [22] using the total lung volume and $\alpha/\beta = 4.0$ Gy.
[b]Paired, two-tailed Wilcoxon signed-rank test.

CTVs in the BHI and BHE phases, the derived movement was 4.2 ± 2.9 mm (range 0.6–10.1 mm). The two methods were consistent on a patient-by-patient level, as seen in Supplementary Table 1. The movement was primarily in the anterior–posterior direction. The patients were ordered from 1 to 12 based on the CTV mass center movement amplitude between the BHI and BHE phases. The maximum volume change of the CTV was 3.1 ± 1.6% (range of 1.1–5.7%), based on the CTV mapping, and 3.8 ± 2.6% (range of 0.1–7.8%) based on the originally defined CTVs.

Nominal plan evaluation

All nominal photon and proton (RBE = 1.1) plans fulfilled the clinical goals for the target and the OARs. All of the evaluated metrics for the CTV and OARs were slightly improved using IMPT compared with hybrid IMRT, as seen in Table 1 and Supplementary Table 2, where the evaluation of the dosimetric metrics are stated. Most of the reductions were also statistically significant ($p < .05$). Applying the Wedenberg RBE model resulted in an average RBE of 1.18 for the CTVs (range 1.14–1.21) and an increased HI compared to the generic RBE (Table 1). Due to the low α/β assumptions and the high LET_d within the OARs, the variable Wedenberg RBE model predicted even higher RBEs in the OARs compared to the CTV. RBE values in order of 1.2–2.0 were observed in the OARs beyond the target volume. This affected some statistically significant results obtained with the constant RBE, as seen in Supplementary Table 2 for, e.g., $V_{5Gy\ (RBE)}$ for the heart and $V_{10Gy\ (RBE)}$ for the left lung, where the reduction compared to photons no longer was statistically significant when applying the Wedenberg RBE model. The statistically significant reduction of about 20% on average of the integral dose to the normal tissue using IMPT instead of hybrid IMRT, was also deteriorated when applying the variable RBE, whereas the lung NTCP was not. The enhanced RBE predicted by the Wedenberg RBE model is illustrated in Figure 1 for the CTV and the left lung through the nominal DVHs for all 12 patients, and in Figure 2 where the proton dose distribution using RBE = 1.1 and the Wedenberg RBE model, the LET_d distribution and the dose difference are shown for a representative patient.

Robustness evaluation

When assuming RBE = 1.1, all IMPT plans fulfilled the CTV robustness criteria for the calculations on the FB CT alone and for the simulated breathing motion scenario (Figure 3(a,c)). Two of the patients with the largest breathing motion (8 and 12) did not fulfill the $D_{98\%}$ robustness criterion for at least one extreme phase, and two patients (8 and 9) did not fulfill the $D_{2\%}$ robustness criterion. This could be compared with the hybrid IMRT plans where four patients failed at least once the $D_{98\%}$ robustness criterion and five patients at least once the $D_{2\%}$ robustness criterion, as seen in Supplementary Figure 1.

Applying the Wedenberg RBE model with parameter uncertainties included resulted in fulfillment of the $D_{98\%}$ robustness criterion for all patients and scenarios, as seen in Figure 3(b). The $D_{2\%}$ robustness criterion was not fulfilled for any nominal plan due to the average predicted RBE of 1.18, hence all robustness scenarios also failed to meet this criterion (Figure 3(d)). The dominant factor was the uncertainty in the α/β value of the CTV, where the worst-case scenarios occurred when α/β was as low as 1 Gy (the assumed 95% CI was 1.0–6.0 Gy).

For RBE = 1.1, the left lung and heart doses were below the robustness criteria in all cases and only failed the nominal plan criterion for the left lung in the extreme cases for patients 8 and 12 (Figure 4(a,c)). The estimated worst-case mean dose for the LAD stayed below 10 Gy (RBE) for all scenarios studied using the constant RBE (Figure 4(e)) and the maximum calculated lung NTCP was 0.7%. Applying the Wedenberg RBE model increased all worst-case OAR doses. This is due to the low worst-case α/β of about 1.5–2.0 Gy and the high LET_d, as all OARs studied were situated beyond the distal edge of the incoming beams. Despite this, the robustness criterion for the left lung was fulfilled for all but two cases and the nominal plan criterion was met for the mean heart dose for all

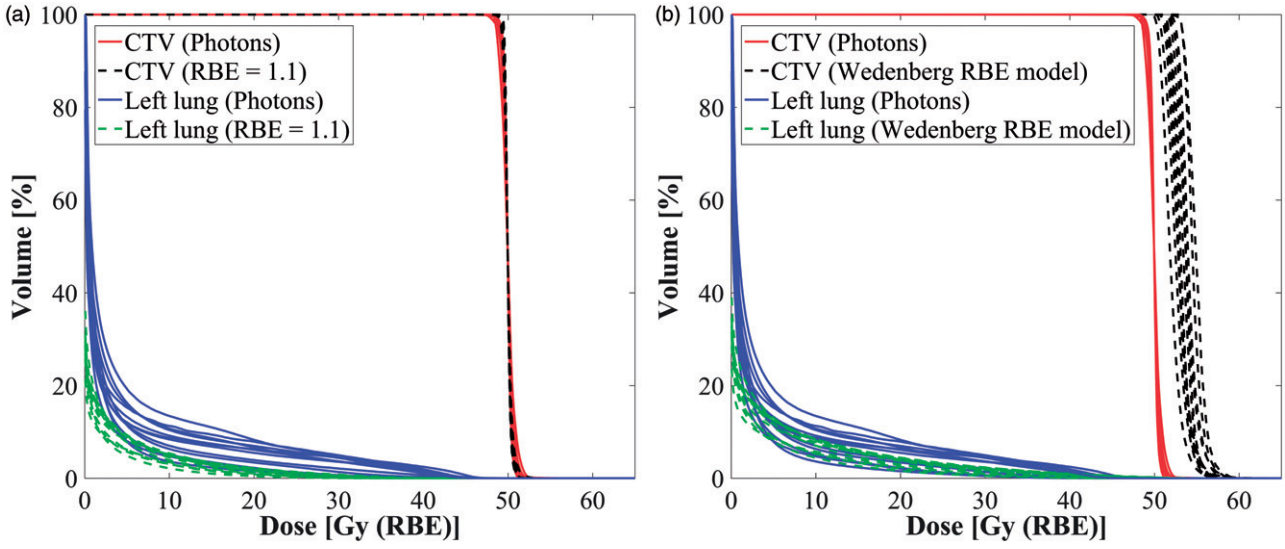

Figure 1. Nominal DVHs for the CTV and left lung for all 12 patients. Panel (a) shows the photon plans together with the proton plans assuming RBE = 1.1, whereas panel (b) shows the photon plans and the protons plans using the Wedenberg RBE model assuming $\alpha/\beta = 3.5$ Gy for the CTV and 4.0 Gy for the left lung.

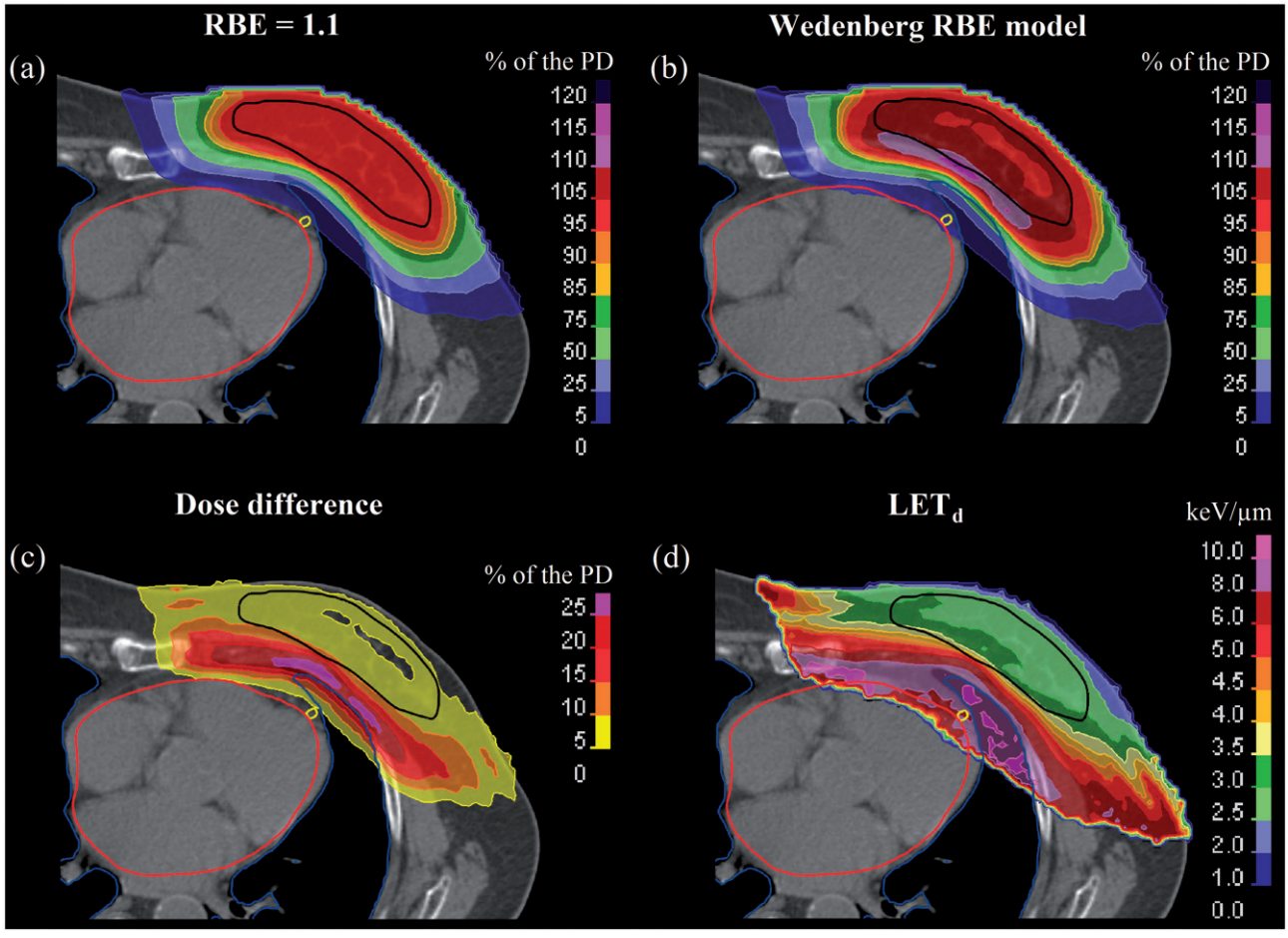

Figure 2. Representative transverse slices for one patient. Panel (a) shows the dose distribution using RBE = 1.1 and panel (b) the dose distribution using the Wedenberg RBE model assuming an α/β of 3.5 Gy for the CTV, 4.0 Gy for the lungs and 3.0 Gy for the remaining normal tissues. Panel (c) shows the dose difference between panel (a) and (b), whereas panel (d) shows the LET_d distribution. The PD was 50 Gy (RBE) in 25 fractions.

scenarios (Figure 4(b,d)). The worst-case mean dose for the LAD stayed below 10 Gy (RBE) in a majority of the studied cases (Figure 4(f)) and the calculated lung NTCP was below 1% in all but one case (1.4% for patient 8 for the BHI evaluation).

The hybrid IMRT fulfilled the nominal plan criteria in most cases for the left lung and heart doses and the robustness criteria in all cases (Supplementary Figures 2a and 2b). The LAD mean dose was larger than 20 Gy (RBE) in some evaluated cases (Supplementary Figure 2c), which was higher

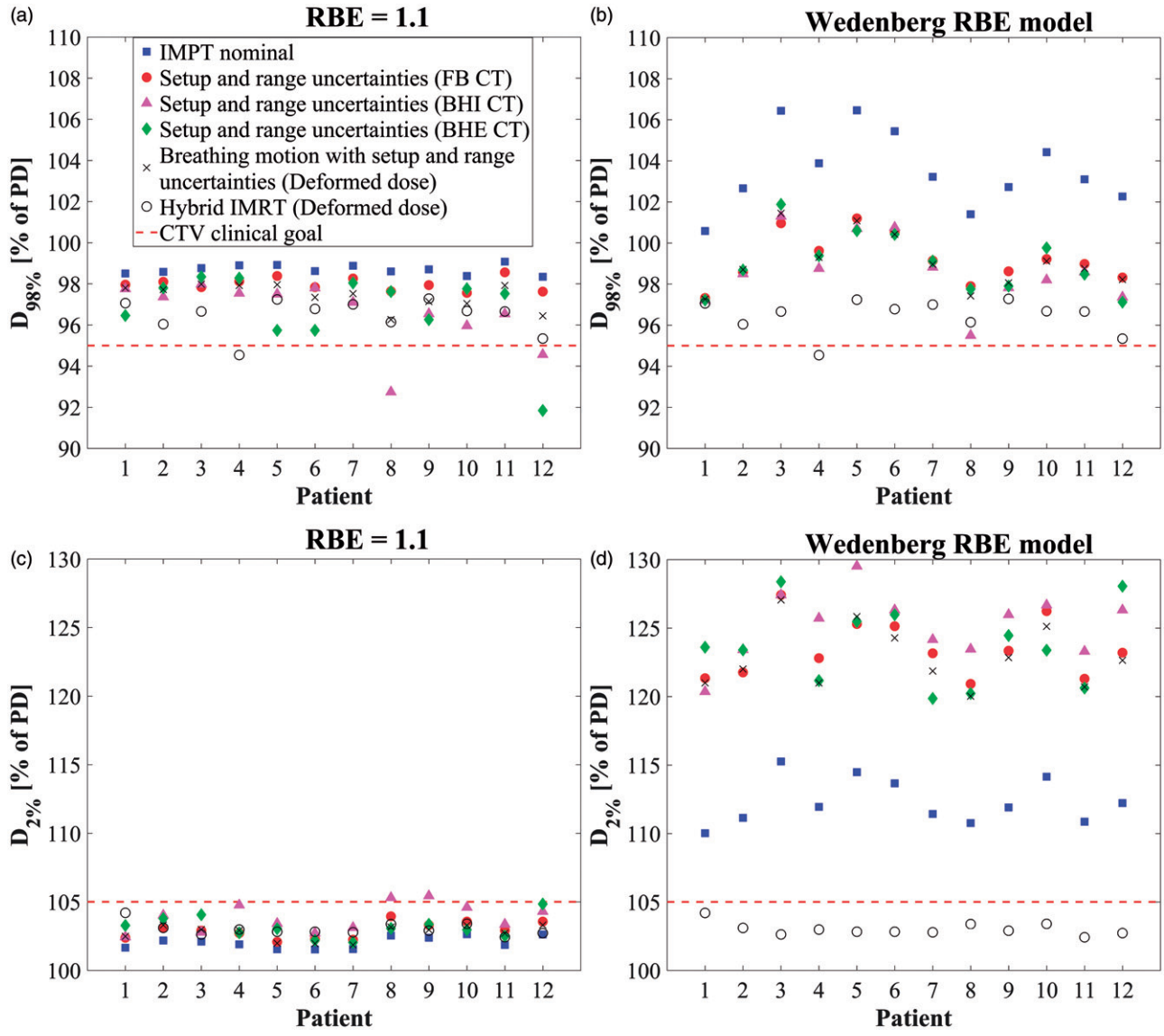

Figure 3. Robustness evaluation of the $D_{98\%}$ and $D_{2\%}$ for the CTV. Panels (a) and (c) show the worst-case values for all scenarios for the IMPT plans assuming RBE =1.1. Panels (b) and (d) show the worst-case values assuming the Wedenberg RBE model with parameter uncertainties included. The worst-case evaluation of the robustness against breathing motion combined with setup uncertainty for the hybrid IMRT plans is shown in all panels.

than the worst-case scenarios for the IMPT plans using the Wedenberg RBE model. The maximum calculated lung NTCP was 0.6% for the hybrid IMRT plans.

Discussion

The potential impact on plan quality of including breathing motion and a variable RBE has been investigated for radiotherapy of breast cancer. Both the IMPT (RBE = 1.1) and hybrid IMRT plans were shown to be robust against breathing motion combined with setup and range uncertainties, both in terms of target coverage and OAR doses. This is in line with previous findings for IMPT breast plans [8,9,23]. The robustness of the CTV coverage against setup and range uncertainties could be explained by the use of adequate robustness parameters in the optimization in this study (5 mm/3%). The robustness against breathing motion was due to the generally small anatomical changes introduced by the breathing motion of a few millimeters, combined with that the dominant direction of the motion was correlating with the beam directions. This correlation is illustrated in Supplementary Figure 3 where the deformation vectors for a DIR between the BHI and BHE CT are shown for one representative patient together with the beam directions. Only in the extreme cases, where the whole treatment was simulated on an extreme breathing phase for patients with large breathing motion, it seemed likely that the clinical goals were violated for the IMPT plans using RBE = 1.1 in this study. As the target motion of about 1–12 mm observed for this patient cohort is inline, or even slightly larger, compared with previous studies evaluating FB motion of breast cancer patients [23–25], it seems justified to draw these conclusions based on the use of the BHI and BHE as surrogates for the extreme phases of FB patterns. When simulating a treatment in FB, by mapping the doses from the three CT scans, the IMPT plans (RBE = 1.1) fulfilled all nominal plan criteria for all patients whereas the hybrid IMRT plans only failed the CTV coverage and left lung criteria in one case each, as seen in

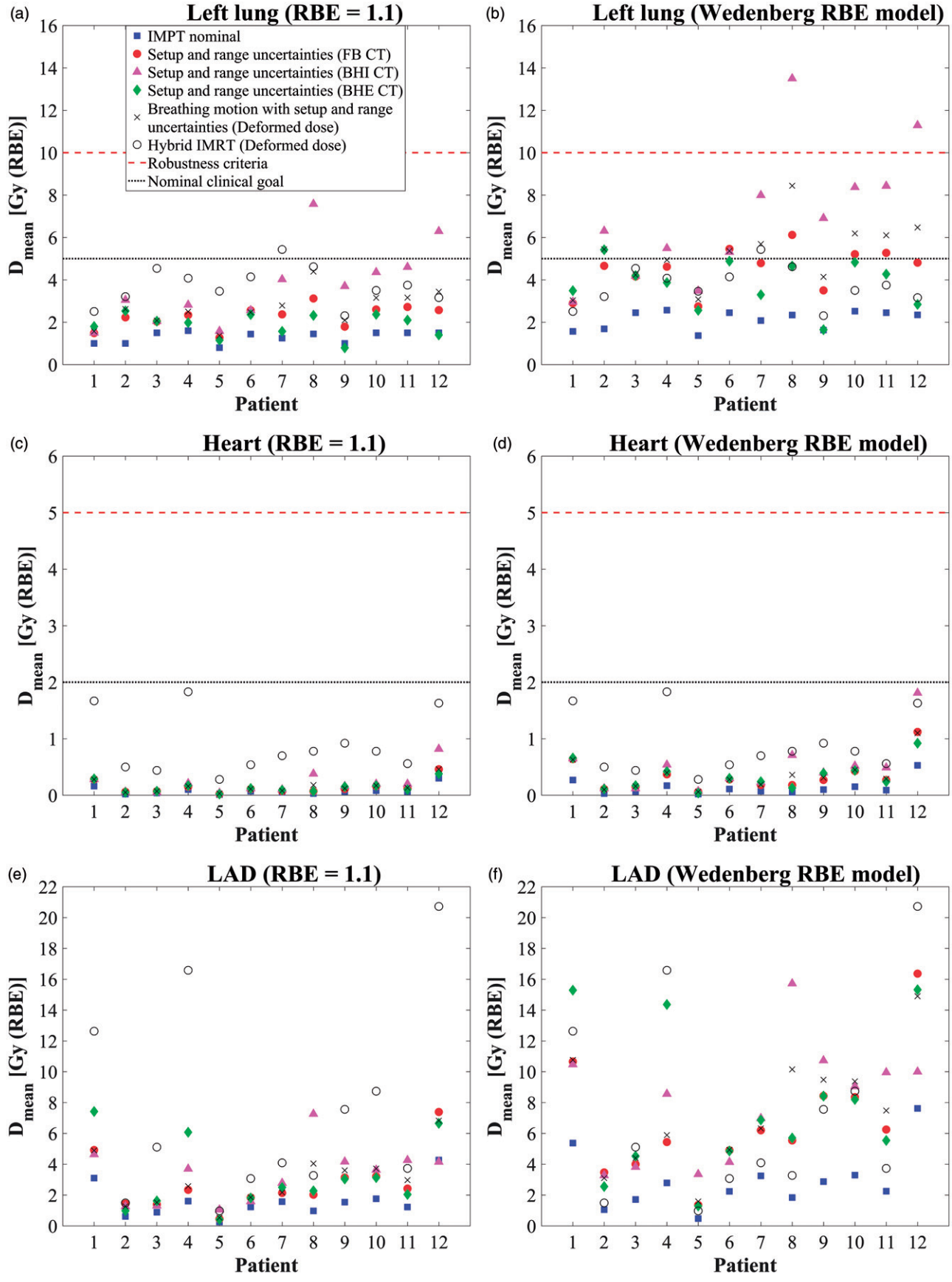

Figure 4. Robustness evaluation of the D_{mean} for the left lung, heart and LAD. Panels (a), (c) and (e) show the worst-case values for all scenarios for the IMPT plans assuming RBE = 1.1. Panels (b), (d) and (f) show the worst-case values assuming the Wedenberg RBE model with parameter uncertainties included. The worst-case evaluation of the robustness against breathing motion combined with setup uncertainty for the hybrid IMRT plans is shown in all panels.

Figures 3 and 4. Furthermore, as breathing patterns showed great variability, the extreme cases identified in this analysis are likely to be considerably diluted for fractionated schedules with many fractions.

As the variable RBE increased the predicted CTV and OAR doses in all scenarios, it could be used to estimate worst-case scenarios in a plan comparison between protons and photons. The magnitude of the increased CTV dose was highly dependent on the breast thickness as the average LET_d increased with smaller modulation width. This is reflected in Figure 1(b) where the highest CTV doses were observed for the thinnest targets (breast thickness range of 2.5–10.5 cm for the cohort). This behavior is well known [2] and suggests that the RBE increase is the largest for patients with thin targets (about 10% increase compared with RBE = 1.1). This opens the potential of lowering the physical doses for such targets, with the consequential possibility of lowering, e.g., lung NTCP even further without decreasing the TCP. Such an approach, using a re-optimization of the physical dose based on the LET_d distribution, has previously been proposed for prostate cancer [7], but could easily be applied to breast cancer cases. However, considering the uncertainty in the predicted RBE, such lowering of the physical dose should be conservatively used in the clinic at this stage [26].

The dosimetric impact of the increased RBE predicted in the normal tissues was minor for the nominal plans in this study due to the low physical OAR doses. However, as almost all normal tissues were situated beyond the distal edge of the beams, high LET_d values were calculated there. This led to an increase in the predicted integral dose to the normal tissues of about 20% compared with RBE = 1.1. Moreover, when the RBE uncertainties were included in the robustness evaluation along with breathing motion, setup and range uncertainties, substantially higher worst-case CTV and OAR doses were predicted. It should be pointed out that these scenarios were predicted under the assumption of very low α/β values (1–2 Gy) combined with the worst-case scenarios in terms of overshot/undershoot, setup and breathing phase. In other words, these scenarios are highly unlikely. However, by evaluating these scenarios, this study indicates that even when including the variable RBE and its uncertainties, the quality of the IMPT plans seems to be at least comparable to photon plans in most aspects. This happens even though the OAR doses for the photon plans in this study were substantially lower compared to other similar studies [9–12]. For example, the mean dose to the left lung and heart was reported as 3.1 and 0.8 Gy in this study (Table 1), respectively, whereas values around 5–8 Gy and 1–5 Gy have been seen in other similar studies [9–12].

Other aspects to consider are the choice of RBE model and the dose dependence for the variable RBE. This study was done for 2 Gy (RBE) per fraction using one variable RBE model, but as the dose per fraction increases, the difference between most variable RBE models and RBE = 1.1 generally decreases [2,5,7,8]. This was also previously demonstrated for a few breast cases, showing that the predicted RBE and the expected worst-case doses decreased as the fractionation dose increased using two different RBE models [8]. Hence, the extrapolation of the results from this study to hypofractionated schedules should be pursued with caution as the magnitude is likely to be reduced compared to 2 Gy (RBE) per fraction. On the other hand, even though the magnitude of the effects observed in this study is dependent on the RBE model, the findings that the variable RBE predicts higher doses to the CTV and OARs are likely to be model independent as the increased RBE with lower α/β, lower dose and higher LET is common for most RBE models [2,5,7,8].

As proton beams, unlike to photon beams, do not have dose build-up at the skin surface, the potentially increased skin dose could be a concern. This has not been investigated in the present study, but a recent study by Tommasino et al. [12] showed that the expected skin toxicity is actually lower for IMPT compared with IMRT, using a similar IMPT field arrangement as in this study. As indicated by Figure 2(c), this is likely to be valid even if using a variable RBE, as no substantial dose increase was predicted for the skin. If the skin was considered as a structure of interest in the optimization, the doses could be lowered even further [12].

In conclusion, proton radiotherapy for breast cancer appears to be a robust treatment approach. Potential errors caused by breathing motion combined with setup and range uncertainties appear to have a minor impact on the plan quality, both in terms of target coverage and OAR doses. On the other hand, the variable RBE might degrade the potential benefit of protons for breast cancer. However, this could probably be neglected in most cases with normal breathing and where the physical OAR doses are low. Nevertheless, the biological evaluation of proton plans taking into account the variable RBE is recommended in a NTCP-based plan comparison to identify the outlier cases at risk for high burden to the OARs.

Disclosure statement

Jakob Ödén is part-time employed as an industrial PhD student at RaySearch Laboratories. Kjell Eriksson is shareholder of RaySearch Laboratories and full-time employed as Chief Science Officer at RaySearch Laboratories.

Funding

Financial support from the Cancer Research Funds of Radiumhemmet is gratefully acknowledged.

ORCID

Anna Maria Flejmer http://orcid.org/0000-0001-8425-8110
Alexandru Dasu http://orcid.org/0000-0001-8171-2541

References

[1] Langendijk JA, Lambin P, De Ruysscher D, et al. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol. 2013;107:267–273.
[2] Paganetti H. Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint,

dose, and linear energy transfer. Phys Med Biol. 2014;59: R419–R472.
[3] Peeler CR, Mirkovic D, Titt U, et al. Clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma. Radiother Oncol. 2016;121:395–401.
[4] Fredriksson A, Forsgren A, Hårdemark B. Minimax optimization for handling range and setup uncertainties in proton therapy. Med Phys. 2011;38:1672–1684.
[5] Dasu A, Toma-Dasu I. Impact of variable RBE on proton fractionation. Med Phys. 2013;40:11705.
[6] Wedenberg M, Toma-Dasu I. Disregarding RBE variation in treatment plan comparison may lead to bias in favor of proton plans. Med Phys. 2014;41:91706.
[7] Ödén J, Eriksson K, Toma-Dasu I. Inclusion of a variable RBE into proton and photon plan comparison for various fractionation schedules in prostate radiation therapy. Med Phys. 2017;44: 810–822.
[8] Ödén J, Eriksson K, Toma-Dasu I. Incorporation of relative biological effectiveness uncertainties into proton plan robustness evaluation. Acta Oncol. 2017;56:769–778.
[9] Ares C, Khan S, MacArtain AM, et al. Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relevant improvements? Int J Radiat Oncol Biol Phys. 2010;76:685–697.
[10] Lin LL, Vennarini S, Dimofte A, et al. Proton beam versus photon beam dose to the heart and left anterior descending artery for left-sided breast cancer. Acta Oncol. 2015;54:1032–1039.
[11] Flejmer AM, Edvardsson A, Dohlmar F, et al. Respiratory gating for proton beam scanning versus photon 3D-CRT for breast cancer radiotherapy. Acta Oncol. 2016;55:577–583.
[12] Tommasino F, Durante M, D'avino V, et al. Model-based approach for quantitative estimates of skin, heart, and lung toxicity risk for left-side photon and proton irradiation after breast-conserving surgery. Acta Oncol. 2017;56:730–736.
[13] Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet. 2011;378:1707–1716.
[14] Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368:987–998.
[15] Weistrand O, Svensson S. The ANACONDA algorithm for deformable image registration in radiotherapy. Med Phys. 2015;42:40–53.
[16] Xie X, Ouyang S, Wang H, et al. Dosimetric comparison of left-sided whole breast irradiation with 3D-CRT, IP-IMRT and hybrid IMRT. Oncol Rep. 2014;31:2195–2205.
[17] Wedenberg M, Lind BK, Hårdemark B. A model for the relative biological effectiveness of protons: the tissue specific parameter α/β of photons is a predictor for the sensitivity to LET changes. Acta Oncol. 2013;52:580–588.
[18] Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14: 1086–1094.
[19] Bentzen SM, Skoczylas JZ, Bernier J. Quantitative clinical radiobiology of early and late lung reactions. Int J Radiat Biol. 2000;76: 453–462.
[20] Joiner MC, van der Kogel A, editors. Basic clinical radiobiology. 4th ed. London: Hodder Arnold; 2009. p. 102–134.
[21] Lowe M, Albertini F, Aitkenhead A, et al. Incorporating the effect of fractionation in the evaluation of proton plan robustness to setup errors. Phys Med Biol. 2016;61:413–429.
[22] Seppenwoolde Y, Lebesque JV, De Jaeger K, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. Int J Radiat Oncol Biol Phys. 2003;55:724–735.
[23] Depauw N, Batin E, Daartz J, et al. A novel approach to postmastectomy radiation therapy using scanned proton beams. Int J Radiat Oncol Biol Phys. 2015;91:427–434.
[24] Thomsen MS, Harrov U, Fledelius W, et al. Inter- and intra-fraction geometric errors in daily image-guided radiotherapy of free-breathing breast cancer patients measured with continuous portal imaging. Acta Oncol. 2014;53:802–808.
[25] Wang W, Li JB, Hu HG, et al. Correlation between target motion and the dosimetric variance of breast and organ at risk during whole breast radiotherapy using 4DCT. Radiat Oncol. 2013;8:11.
[26] Grassberger C, Paganetti H. Varying relative biological effectiveness in proton therapy: knowledge gaps versus clinical significance. Acta Oncol. 2017;56:761–762.