



Original Article

Inverse radiotherapy planning based on bioeffect modelling for locally advanced left-sided breast cancer[☆]



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ABSTRACT

Background and purpose: Treatment planning of radiotherapy (RT) for left-sided breast cancer is a challenging case. Several competing concerns are incorporated at present through protocol-defined dose–volume constraints, e.g. cardiac exposure and target coverage. Such constraints are limited by neglecting patient-specific risk factors (RFs). We propose an alternative RT planning method based solely on bioeffect models to minimize the estimated risks of breast cancer recurrence (BCR) and radiation-induced mortality endpoints considering patient-specific factors.

Methods and materials: Thirty-nine patients with left-sided breast cancer treated with comprehensive post-lumpectomy loco-regional conformal RT were included. An in-house particle swarm optimization (PSO) engine was used to choose fields from a large set of predefined fields and optimize monitor units to minimize the total risk of BCR and mortality caused by radiation-induced ischaemic heart disease (IHD), secondary lung cancer (SLC) and secondary breast cancer (SBC). Risk models included patient age, smoking status and cardiac risk and were developed using published multi-institutional data.

Results: For the clinical plans the normal tissue complication probability, i.e. summed risk of IHD, SLC and SBC, was <3.7% and the risk of BCR was <6.1% for all patients. Median total decrease in mortality or recurrence achieved with individualized PSO plans was 0.4% (range, 0.06–2.0%)/0.5% (range, 0.11–2.2%) without/with risk factors.

Conclusions: Inverse RT plan optimization using bioeffect probability models allows individualization according to patient-specific risk factors. The modelled benefit when compared to clinical plans is, however, modest in most patients, demonstrating that current clinical plans are close to optimal. Larger gains may be achievable with morbidity endpoints rather than mortality.

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Breast cancer is the most prevalent cancer among women in the U.S. with a 5 year survival of 90% [1]. In January 2018, there were more than 3.4 million breast cancer survivors in the U.S. alone [1]. This means that though the risk of developing a radiation-induced late effect is low, even small changes in that probability have a large impact at a societal level: a 0.1% change in mortality will cause the premature death of 3400 breast cancer survivors, emphasizing the importance of continued improvement of radiotherapy (RT) beyond the current state of the art.

The randomized EORTC 22922/10925 and NCIC-CTG MA.20 trials showed that irradiation of lymph nodes including the ipsilateral internal mammary nodes (IMN) improves tumour control in selected breast cancer patients [2,3], consistent with results from the population-based DBCG-IMN study [4]. In left-sided cases, however, this will expose the heart to radiation, which in turn, increases the risk of coronary heart disease [5]. Furthermore, IMN irradiation leads to increased lung dose and subsequent increased risk of secondary lung cancer [6,7].

The goal in RT planning is to maximize the therapeutic ratio by giving a sufficient dose to the target while sparing organs at risk (OARs) to increase the probability of tumour control and reducing the risk of radiation-induced toxicity. In current RT planning for left-sided breast cancer, the IMN dose distribution will often be compromised when the dose to the heart and lung exceeds the limits defined by dose–volume constraints in clinical treatment

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guidelines. These constraints, however, are population-based quantities defined for organs or substructures separately and do not account for patient-specific risk factors (such as age, comorbidities and lifestyle) that have shown to impact severity and mortality risk of radiation-induced cardiotoxicity (see [5] as an example).

The current practice of using defined dose–volume constraints generally fails to explicitly consider patient-specific factors in a quantitative way. In this study, we propose a planning method based entirely on bioeffect probability models that estimate individual risks of breast cancer recurrence (BCR) and death from secondary cancer and cardiotoxicity during optimization. These models incorporate patient age and other risk factors (RFs).

Methods and materials

Patients

All patients with left-sided breast cancer referred for post-lumpectomy loco-regional RT at Rigshospitalet in 2015 and treated according to a standard protocol were selected for this retrospective study (41 patients) [8]. Two patients were treated with a hybrid plan (a combination of volumetric modulated arc therapy (VMAT) and 3D conformal radiotherapy (3DCRT)) and were excluded from this retrospective study. The remaining 39 patients received 3DCRT using mono-isocentric tangential opposing fields and supraclavicular fields with beam junction at the isocentre. Six to 11 fields were used with beam energies of 6MV supplemented by 18MV. See an example of field setup in Fig. 1a. The clinical target volume (CTV) consisted of the whole breast and regional lymph nodes (IMN, level II–IV and interpectoral) as per ESTRO guidelines [9]. Heart and left anterior descending artery (LAD) were contoured according to guidelines [10], and lungs were contoured using an automatic segmentation tool. No planning target volumes were used. Instead, the multileaf collimator (MLC) was fitted to the CTV structure with a margin of 1 cm for each field. The MLC was afterwards adjusted to shield the heart and LAD for most fields. Based on the opinions of clinicians performing treatment planning, compromise in shielding of heart and LAD could vary in a case by case level. The prescription dose for all patients was 50 Gy (25 fractions of 2 Gy). The clinical planning objective was to cover the whole breast with at least 95% and maximum 107% of the prescribed dose and to cover the lymph nodes with at least 90% and maximum 107% of the prescribed dose. All patients were treated in deep-inspiration breath-hold following departmental guidelines [11]. The median patient age was 52 years (range: 26–79). The total volume of the CTV ranged between 171 cc and 2881 cc.

Multifield setup

A multifield beam set was prepared to allow the optimization algorithm to choose from a field-set in the following way: Four copies of each clinical field were created. For tangential fields, the gantry was rotated 10 and 20 degrees towards the axilla and 5 and 10 degrees towards the contralateral breast to avoid irradiating the contralateral breast. For supraclavicular fields, the gantry was rotated 10 and 20 degrees towards the axilla and 10 and 20 degrees towards the contralateral breast (see Fig. 1b). The MLC was shaped to act similar to the clinical field in covering targets and sparing heart and LAD, i.e. the MLC was fitted to the CTV with a margin of 1 cm and the MLC was adjusted to shield the heart and LAD if that was done in the clinical field. An extra copy of the field was created for all fields whenever IMN was compromised (heart and LAD shielding) and for the copied field the MLC was fitted to the CTV with a margin of 1 cm to ensure adequate coverage with-

out shielding heart and LAD. Field dose deposition matrices were calculated in Eclipse V13.6 Treatment Planning System (Varian Medical Systems, Palo Alto, CA) with the Anisotropic Analytical Algorithm.

Bioeffect modelling

In the presented inverse RT planning method, the plans were optimized towards minimizing the total risk of BCR or death within 10 years after treatment and mortality from radiation-induced ischaemic heart disease (IHD), secondary lung cancer (SLC) and secondary breast cancer (SBC) by the age of 80 years. All risks were weighted equally, i.e. objective function was: $\text{Risk}_{\text{total}} = \text{Risk}_{\text{BCR}} + \text{Risk}_{\text{IHD}} + \text{Risk}_{\text{SLC}} + \text{Risk}_{\text{SBC}}$.

For BCR risk modelling the CTV was divided into two targets: (1) IMN and (2) primary CTV defined as whole breast, level II–IV lymph nodes and interpectoral lymph nodes. The BCR risk and disease-free survival (DFS) were estimated from a linear no-threshold model of the hazard ratio of failure fitted to the results of published randomized trials as a function of dose coverage of IMN [2,3,12] and primary CTV [13]. The dose–effect was truncated at the prescription dose on a voxel-by-voxel level for objective function calculation to prevent the model to benefit from overdosing the target. Mean doses to IMN and primary CTV were used as target model input parameters.

The BCR risk modelling is presented in detail in [14] and Appendix A.

The IHD risk model used interpolated excess absolute risk estimates of radiation-induced IHD events at age 80 for patients with and without cardiac RFs from Table S12 in the supplementary materials of the paper by Darby et al. [5]. Cardiac RFs were defined as history of circulatory disease, diabetes, smoking and obesity [5]. The input variables were mean heart dose (MHD), patient age and whether the patient had pre-existing cardiac RFs or not [8].

The risks of SLC and SBC were modelled based on the method presented by Brodin et al. [15] using dose–response data from Grantzau et al. [7] and Travis et al [16]. The SBC dose–response data originate from a Hodgkin lymphoma cohort since no relevant dose–response data from breast cancer patients were available, the model input variables include mean breast dose (MBD) to the contralateral breast, patient age, and estimated DFS. The SLC model input parameters were mean lung dose (MLD) to the whole lung, patient age, smoking status, and estimated DFS from the target model.

The normal tissue complication probability (NTCP) models are presented in detail in [14] and Appendix B.

Plan optimization

The inverse risk-based RT planning was performed with an in-house optimization algorithm using particle swarm optimization (PSO) [17,18]. The optimization goal was to minimize the objective function (the total risk) by choosing fields from the created set of fields including the clinical fields and optimizing monitor units (MUs). PSO search agents (known as particles) searched the solution space for the optimal solution. Each particle memorized the best solution they found and communicated with the other particles to find the global optimal solution. Thirty particles over 100 iterations were used for this study's optimization. Fields with MU below 5 were not accepted. The inverse planning optimization workflow is explained in detail in [14].

All patient plans were optimized twice: assuming the patient had no RFs (i.e. no cardiac risk factors including smoking) and assuming the patient had 1 or more RFs (i.e. the patient is a smoker and may have other cardiac RFs). A paired, two-sided *t*-test was

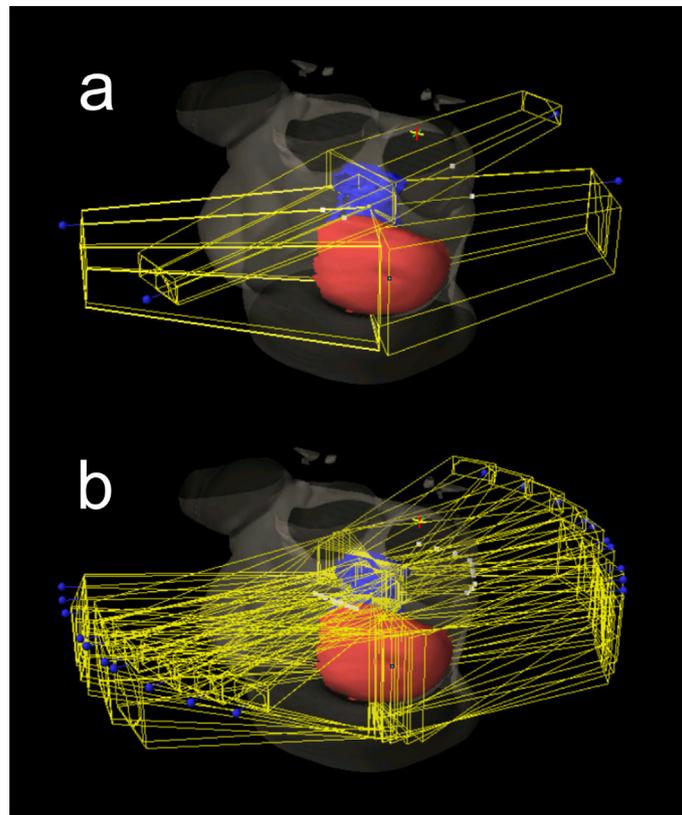


Fig. 1. Example of field setup with tangential and supraclavicular fields: clinical field setup (a) and multifield setup (b).

used to evaluate the differences in mean doses to OARs between PSO plans with no RFs and PSO plan with at least 1 RF.

Results

The median number of used fields in the individualized PSO plans was 6 (range, 4–10) with no RFs and 5 (range, 3–9) with RFs. Forty percent of the fields used in the individualized PSO plans were clinical fields.

For the clinical plans, median mean dose to heart, lungs and contralateral breast was 1.7 Gy (range, 0.2–4.0 Gy), 7.4 Gy (range, 4.4–8.3 Gy) and 0.6 Gy (range, 0.15–4.7 Gy). Mean doses to the OARs and target structures assuming no RFs and ≥ 1 RFs are shown in Fig. 2. Mean dose to the heart and lungs was reduced in the individualized PSO plans when including RFs compared to no RF (paired *t*-test, $p < 0.05$); i.e., the dose was distributed away from heart and lungs in high-risk patients. The sparing of heart and lungs resulted in a lower mean dose to the target structures, especially IMN (see Fig. 3).

For the clinical plans, the NTCP, i.e. the median summed risk of IHD, SLC and SBC, was 1.3% (range, 0.06–2.0%) with no RFs and 2.5% (range, 0.15–3.7%) with RFs (also illustrated in Fig. 4). The median estimated risk of BCR was 2.0% (0.8–6.1%) for all clinical plans. The median reduction in total risk achieved with the individualized PSO plans was 0.4% (range, 0.06–2.0%) assuming no RFs and 0.5% (range, 0.11–2.2%) assuming RFs (also illustrated in Fig. 5). Six of the patients had a modelled reduction in total risk of more than 1% in both scenarios.

Discussion

This study presents the concept of RT optimization entirely based on bioeffect models across several outcomes while account-

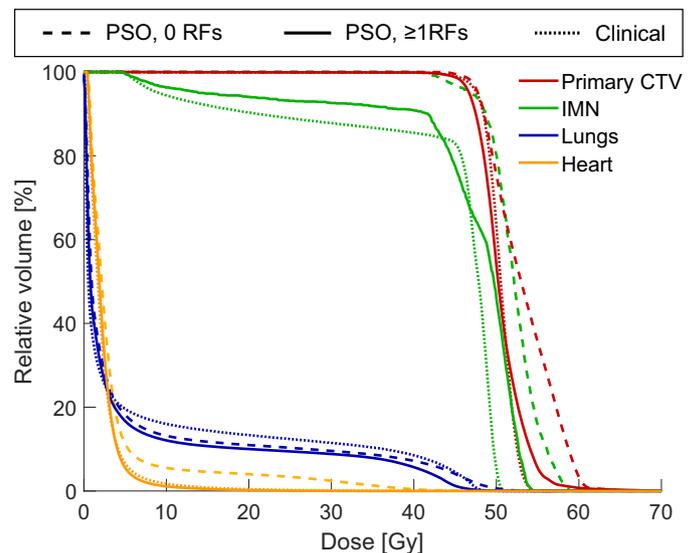


Fig. 2. Dose–volume histogram for 1 patient comparing the PSO plan with no RFs (dashed lines), the PSO plan with 1 or more RFs (solid lines) and the clinical plan (dotted lines). The reduction in total risk (BCR + NTCP) relative to the clinical plan was 1.8% for both RF scenarios. Abbreviations: PSO, particle swarm optimization; BCR, breast cancer recurrence; NTCP, normal tissue complication probability; RF, risk factor; IMN, internal mammary nodes; CTV, clinical target volume.

ing for individual risk factors. We demonstrate face validity of the method by showing that the optimized dose plans protect the critical organs in patients with elevated risk of toxicity. However, the absolute benefit on these severe endpoints is limited in an individual case and it should also be stressed that the approach has important limitations:

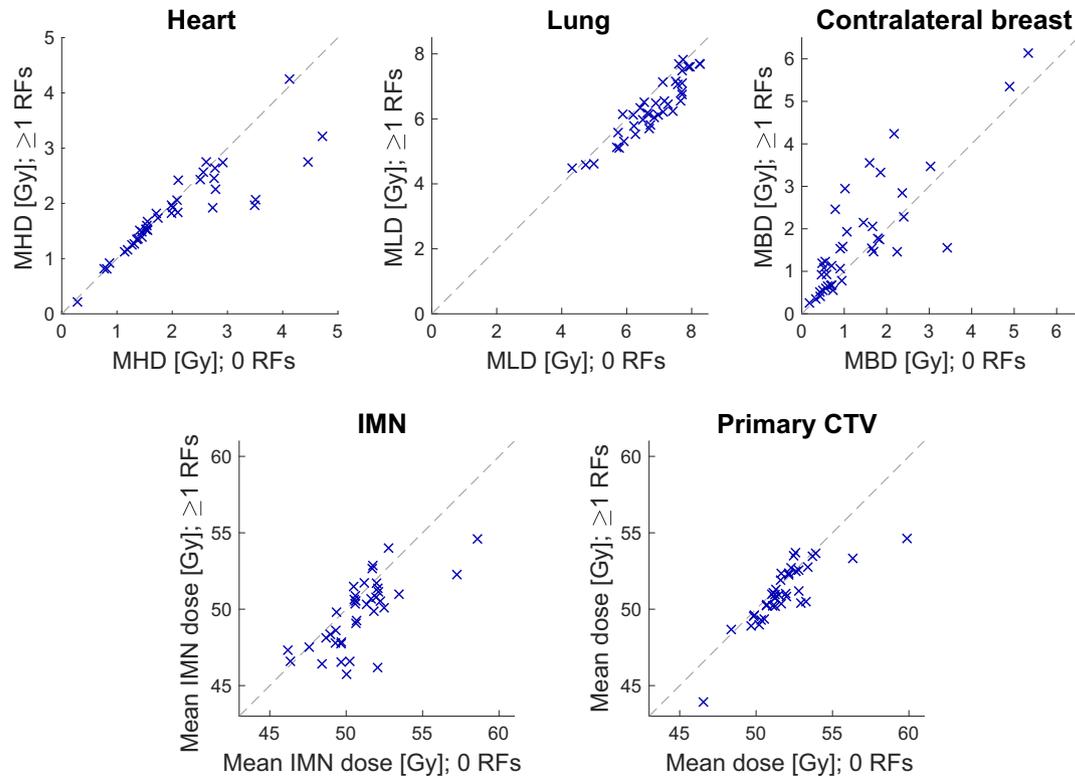


Fig. 3. All plots show mean dose for individualized PSO plans for 0 RFs (x-axis) and ≥ 1 RFs (y-axis). Dose is moved away from lung and heart in patients with risk factors. Dose to IMN and primary CTV (whole breast + supraclavicular and axillary lymph nodes) is in most cases compromised more in patients with RFs. Abbreviations: RF, risk factor; MHD, mean heart dose; MLD, mean lung dose; MBD, mean breast dose; IMN, internal mammary nodes; CTV, clinical target volume.

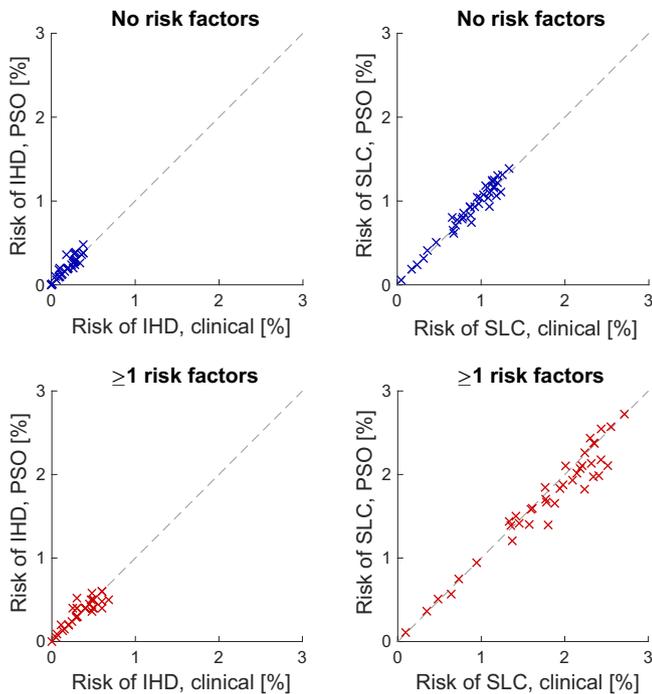


Fig. 4. Risk of IHD (left panels) and SLC (right panels) for clinical plans (x-axis) vs PSO plans (y-axis). Upper panels show risk estimates assuming no risk factors and lower panels show risk estimates assuming 1 or more risk factors. Abbreviations: IHD, aisaemic heart disease; SLC, secondary lung cancer.

First, there is lack of knowledge on which dose metrics and sub-structures are best at predicting outcome. In this study, the NTCP models used mean dose to heart, lungs and contralateral breast.

Second, the impact of patient-specific risk factors on the different outcomes is not fully elucidated albeit may be improved over time using meta-analysis methods [19,20]. In this study, age, smoking status and cardiac risk factors were used. Third, while the optimizing engine gained no benefit by irradiating each voxel in the target more than 50 Gy, in some cases the algorithm resulted in hotspots in the target which would not normally – rightly or not – be accepted in a clinical plan. Such problems could potentially be avoided by including low-grade endpoints as hotspots have been associated with inferior cosmetics [21]. However, trading less severe adverse events for tumour control comes with a number of challenges. Also, compiling a comprehensive list of normal tissue endpoints to account for all regions in the body is challenging and weighting these against each other even more so. Nevertheless, these challenges are inherent to the complexity of radiotherapy plan choice at its core. The weakest part of the modelling is probably related to the risk of recurrence: We chose to model the effect of uniform irradiation at varying levels from the published randomized trials as best available data. However, in the absence of reliable data on the target coverage in the trial cohorts, we assumed the prescribed dose was delivered to the entire target, which may lead to a minor under-estimation of the gain from full target coverage (as the published HR from the trials may be under-estimating the effect of full coverage). This is speculative, however, it is possible that the gain from improving target coverage in practice is slightly better than modelled here.

In the inverse planning process, the field angles were limited to the bundle of fields created in the multifield set. This set included clinical fields and additional fields for which the MLCs were shaped to act similar to the clinical fields in covering the target. In other words, the optimizer was limited by not having access to a full solution space and thus, more optimal PSO plans may exist. Hotspots observed in the PSO plans may also be avoided if the PSO

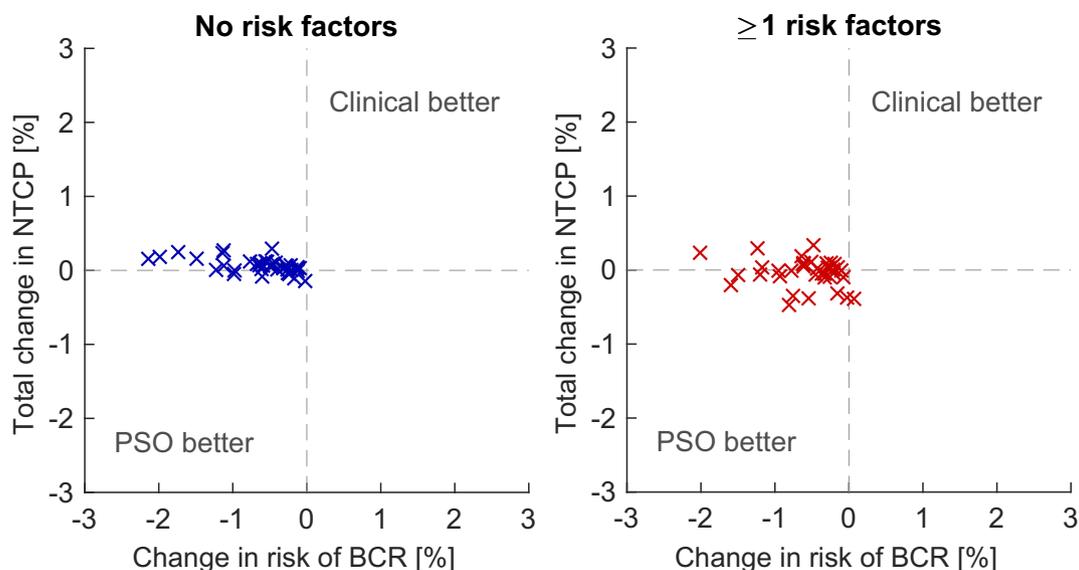


Fig. 5. Change in BCR (x-axis) vs total change in NTCP (y-axis) for clinical vs PSO plans with no risk factors (upper panel) and at least 1 risk factor (lower panel). Change in BCR is defined as the risk estimate of BCR from the clinical plan minus the risk estimate of BCR from the individualized PSO plan. Total change in NTCP is defined as the risk estimate of NTCP from the clinical plan minus the risk estimate of NTCP from the individualized PSO plan. This implies that a negative change in risk of BCR and NTCP is an improvement relative to the clinical plan. Abbreviations: PSO, particle swarm optimization; BCR, breast cancer recurrence; NTCP, normal tissue complication probability.

algorithm has access to full solution space through IMRT or VMAT (see illustration in Appendix C). The next step for this RT planning approach would be to develop the setup so that the PSO engine has access to a larger solution space.

The risks of recurrence and fatal radiation-induced toxicity were modest in most of the clinical plans to begin with, indicating that the clinical forward planned RT approach is close to optimal in most cases. The breast cancer cohort of this study (including the two excluded cases) was re-planned with protons in a previous study [8] modelling the risk of an IHD event and recurrence due to insufficient IMN target. There, we showed that the modelled benefit of using protons relative to photons was modest; only the two hybrid plan cases had a substantial reduction in the risk of cardiotoxicity, indicating that if adequate target coverage can be achieved with 3DCRT only, the predicted benefit of using other planning techniques or other particle type is limited for loco-regional RT in breast cancer patients.

In conclusion, inverse PSO RT planning allowed for individualized plan compromises depending on individual patient characteristics. Such planning approach may lead to field arrangements and dose distributions that differ from the ones routinely used in the clinic, which in turn may lead to improved outcome. The absolute benefit in the postoperative breast cancer case is relatively limited; reflecting in part that the absolute risk of radiation-induced second cancers and cardiac disease as well as cancer-specific mortality is low, and in part that the current RT treatment techniques are near optimal.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.03.018>.

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