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Technical Note

Reduction of heart and lung normal tissue complication probability using automatic beam angle optimization and more generic optimization objectives for breast radiotherapy

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A B S T R A C T

During breast cancer radiotherapy, sparing of healthy tissue is desired. The effect of automatic beam angle optimization and generic dose fall-off objectives on dose and normal tissue complication probabilities was studied. In all patients, dose to lungs and heart showed a mean reduction of 0.4 Gy (range 0.1–1.3 Gy) and 0.2 Gy (range −0.2–0.7 Gy), respectively. These lower doses led to a statistically significant lower cumulative cardiac and lung cancer mortality risk. For smoking patients 40–45 years of age who continue to smoke, it would lead to a reduction from 3.2% ± 0.7% to 2.7% ± 0.6% ($p < 0.001$).

1. Introduction

The use of radiotherapy for breast cancer after breast conserving surgery reduces the risk of recurrence and breast cancer death, as shown by randomized trials [1]. During radiotherapy, however, dose is also delivered to healthy tissue, such as heart and lungs, which can lead to harmful side effects. For dose to the heart, an excess relative risk (ERR) on cardiac mortality of 4.1% per Gy mean heart dose was found [2]. The same study also showed an ERR of 11% per Gy mean lung dose for mortality resulting from radiotherapy induced lung cancer. During the radiotherapy plan optimization dose to these organs at risk (OARs) needs to be avoided as much as possible. With tangential field intensity modulated radiotherapy (IMRT) this can be done by choosing the appropriate beam angles and tweaking the right optimization objectives, among other things. Several studies on automatic beam setting optimization for breast cancer are conducted, showing feasibility to create clinically acceptable plans [3–6]. However, most of the studied techniques are not directly available in commercial treatment planning systems (TPS). This study explores the use of two built-in functions in a TPS. The effect of using automatic beam angle optimization and generic dose fall-off objectives on OAR dose and normal tissue complication probability (NTCP) for heart and lung mortality was investigated.

2. Materials and methods

2.1. Patients

Forty patients, diagnosed with left sided, node negative breast cancer, treated between March 2018 and May 2019 were included in this study. Ethical approval for inclusion was granted by the local ethics committee. Moderate deep inspiration breath hold CT scans and clinical treatment plans were available for all patients, which were treated in breath hold with IMRT, using a prescribed total dose of 40.05 Gy in 15 fractions. RayStation TPS version 8A (RaySearch Medical Laboratories, AB, Stockholm, Sweden) was used to create both clinical and newly optimized plans. Clinical target volume (CTV) and OARs were contoured following the ESTRO guidelines and the planning target volume (PTV) was generated by a 5 mm expansion of the CTV, followed by 5 mm cropping under the skin [7,8].

2.2. Plan optimization

As mentioned in the introduction, it is important to select appropriate beam angles. For the clinical plans, these angles were chosen manually by the planner, based on their experience and tested by trial and error. To create the newly optimized plans, an optimal gantry angle optimization function was utilized. This function was incorporated in the 3D-CRT module of the TPS, which enables finding beam angles during optimization. A new plan is set-up with a standard set of

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objectives, including the dose-fall of function for the OARs, which will be described later. For the PTV, this set contains objectives for a minimum dose of 38.9 Gy, a maximum dose of 42.1 Gy and a uniform dose of 40.1 Gy. Furthermore, the contralateral breast was contoured for all patients and a maximum equivalent uniform dose (EUD) of 1 Gy was set for this contour [9]. The penalty on the contralateral breast prevented it from being included in the radiation beam and thereby reducing dose to the healthy tissue. The optimization in the 3D-CRT module is then initialized with beam angles of 130° and 310. After one optimization run, suitable beam angles were found and could be used in the IMRT plan optimization. Both the clinical as newly optimized plans contained two beams, with a beam energy of either 6 MV or 10 MV. For each newly optimized plan, this energy and the isocenter position were copied from the corresponding clinical plan. The beams consisted of maximum 8 segments, with a minimum segment area of 9 cm^2.

During optimization, the doses to OARs in the clinical plans were reduced by applying a maximum EUD objective for these organs. This function penalized values above the specified maximum, but there was no penalty below this level. Therefore, for each patient, these levels needed to be tweaked manually. Newly optimized plans were created by using the dose fall-off function, which decreased dose far away from the target but allowed higher dose in the buildup region just outside the target. With this function, the dose distribution is more conformal around the target, while hotspots distant from the target volume are avoided. With several user parameters, such as the high and low dose level and low dose distance, a low dose to OARs could be achieved with less manual tweaking, compared to the maximum EUD function. Between the target border and the low dose distance, the dose level decreases linearly from the high to the low dose level. Outside this low dose distance, the low dose level is used as maximum dose. At the start of plan optimization, 42.1 Gy and 0 Gy were chosen as the high and low dose levels, respectively, with a low dose distance of 1 cm for heart and lungs. The same objective was used for the external body contour, but with a low dose level of 20.0 Gy. The user parameters and objectives weights were tweaked during optimization.

2.3. Plan evaluation

After optimization, average heart and lung (both lungs combined) doses were obtained and used to calculate the cumulative risks of radiotherapy induced lung cancer and cardiac mortality at the age of 80 years for both the clinical as the newly optimized plans. These risks were calculated for all age points in the range of 40 to 80 years, with an interval of 5 years. For every age point, the whole patient cohort was considered to have that age. Mortality due to contralateral breast dose was considered to be negligible with values at least 10 times lower than the mortality risks resulting from heart and lung dose. The total cumulative mortality risk was therefore defined as the sum of the risks on radiotherapy induced lung cancer and cardiac mortality. For the calculations, the ERRs found by Taylor et al. were used [2]. To study the effect of dose to OARs for patients with or without risk factors, three patient scenarios were used: 1) no cardiac risk factors and no smoker (C-L-), 2) cardiac risk factors and no smoker (C+L-) and 3) cardiac risk factors and smoker (C+L+). Cardiac risk factors include a history of ischemic heart disease or a circulatory disease other than ischemic heart disease, history of diabetes or COPD, a BMI $\geq$ 30 kg/m^2, current smoker and use of analgesic medication [10]. As smoking is also a cardiac risk factor, there is no C-L+scenario possible. The baseline risk on lung cancer was taken from Taylor et al. [2]. The risk on cardiac mortality was based on the risk on an acute coronary event and cardiac mortality in the Netherlands in 2016. The same underlying model as Darby et al. was used for the calculations. However, the exact numbers of risk differ as they used cardiac death rates for women in 15 Western European countries [10]. Aforementioned models are used as they are both *meta*-analyses of randomized trials. A Wilcoxon signed rank test was performed to investigate significance between doses to OARs of both plans and mortality risks in these scenario's.

3. Results

For the clinical plans, the medial and lateral beams ranged from 300° to 323° and 125° to 145°, respectively. After beam angle optimization, the medial beams ranged from 298° to 326°, with a mean difference (clinical – optimized) of 1.2° (range −6° to 12°). The lateral beams ranged from 121° to 147°, with a mean difference of −1.3° (range −12° to +8°).

In all patients, dose to the lungs was reduced in the newly optimized plans with a mean reduction of 0.4 Gy (range 0.1 to 1.3 Gy). For the heart this mean reduction was 0.2 Gy (range −0.2 to 0.7 Gy), where the dose was increased for one patient. Mean doses to OARs of the clinical and newly optimized plans are shown in Fig. 1. Statistically significant differences were found in doses to heart and lungs between the clinical and re-optimized plans, where the mean dose ± standard deviation (SD) was 2.6 ± 0.7 Gy and 2.2 ± 0.6 Gy to the lungs ($p \leq 0.001$) and 1.3 ± 0.5 Gy and 1.1 ± 0.5 Gy to the heart ($p \leq 0.001$), respectively. All plans had adequate PTV coverage (PTV V95 $\geq$ 97% and V107 $\leq$ 2%), and dose to contralateral breast below 1 Gy (range 0.1 to 0.9 Gy).

For all three patient scenario's, difference in cumulative cardiac and lung cancer mortality risks between the clinical and re-optimized plans were calculated and visualized in Fig. 2. For the re-optimized plans, the cumulative mortality risk was significantly lower ($p \leq 0.001$). The largest difference in cumulative cardiac and lung cancer mortality risk was observed for young patients (40 to 45 years) who are smoking and continue to smoke, where it decreased from 3.2% ± 0.7% for the clinical plans to 2.7% ± 0.6% for the re-optimized plans ($p \leq 0.001$). A median total decrease in mortality of 0.0% (range 0.0–0.2%) without and 0.2% (range 0.0–1.5%) with risk factors was found in our cohort considering the actual patients age at treatment.

4. Discussion

Automatic beam angle optimization and more generic objectives were used to re-optimize treatment plans for whole breast radiotherapy. These objectives contain a dose fall-off function for heart and lungs, which reduces need of manual adjustments. The beam angle is found by utilizing the optimal gantry angle function, available in the TPS. Statistically significant differences in doses to heart and lungs and total

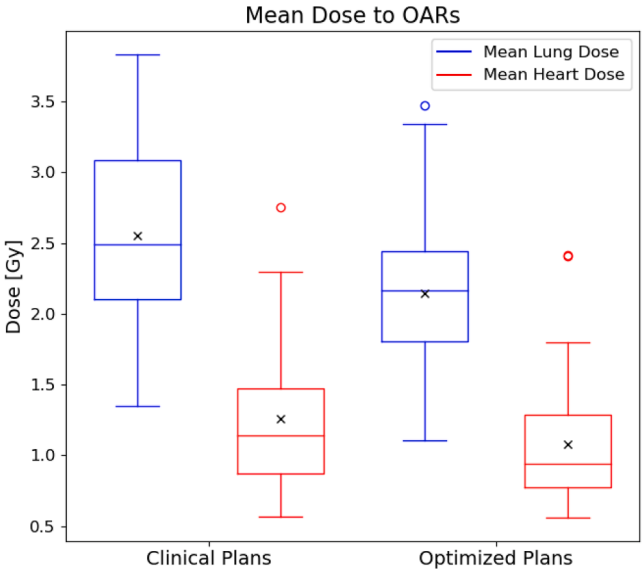

Fig. 1. Boxplots for the mean doses to OARs for the clinical and newly optimized plans. Horizontal lines in boxes are medians, crosses are means, dots are outliers.

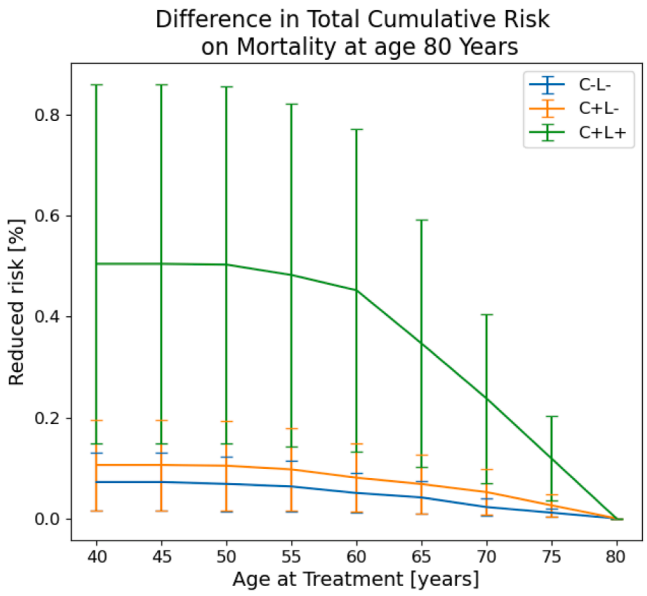

Fig. 2. Differences in total cumulative cardiac and lung cancer mortality risk at age 80 years between the two optimization methods (clinical – newly optimized), for three different patient scenario's; 1) no cardiac risk factors and no smoker (C-L-), 2) cardiac risk factors and no smoker (C+L-) and 3) cardiac risk factors and smoker (C+L+).

cumulative cardiac and lung cancer mortality risks were found between the newly optimized and original clinical plans, favorable to the newly optimized treatment plans.

Several studies on beam angle optimization for IMRT have been performed [4–6]. Zhao et al. used a support vector machine method to find beam placement parameters, by optimizing the posterior plane between the OARs and the target volume [4]. Compared to manually placed beams, a mean difference of -0.61° ($\pm 1.7^{\circ}$) between gantry angles was found, which is a smaller difference than we observed. Although no mean doses to OARs were reported, a decreased dose was reflected by other dosimetric measures. Penninkhof et al. proposed a method where a large patient-specific database is automatically created, with unique combinations of beam angles and treatment isocenter. A plan can then be selected based on the resulting dose to OARs [5]. Wang et al. used an geometry optimization program, penalizing PTV under coverage and lung volume being irradiated, to find feasible gantry angles and isocenter location [6]. This method lead to comparable dose metrics for most organs against clinical plans, with lower mean lung dose for the automatic plans. The latter two studies did not report any data on the gantry angles.

Stick et al. studied plans based on bioeffect modelling for locally advanced left-sided breast cancer [11]. They found a median total decrease in mortality or recurrence of 0.4% (range, 0.6–2.0%)/0.5% (range, 0.1–2.2%) without/with risk factors compared to 0.0% (range 0.0–0.2%) and 0.2% (range 0.0–1.5%) in our study. However, their patient cohort contained patients receiving lymph node irradiation, including internal mammary nodes, which could explain the difference. Furthermore, the difference in decrease can be attributed to the fact that recurrence was not included in our study. Besides, their optimization was performed with an in-house optimization algorithm and can thus not be implemented by others.

The clinical treatment plans were created by various planners with a varying experience, resulting in inter-planner variability. With the new, more generic and standardized method, a smaller inter-observer variation is also expected after clinical introduction. A full inter-observer study is beyond the scope of this technical note.

The risk estimations used in this study are based on the best model parameters available today from *meta*-analysis of clinical trials. However, it has to be mentioned that these parameters do still have quite a large uncertainty.

In conclusion, making use of automatic beam angle optimization and new objectives improved clinical generated plans for left-sided whole breast radiotherapy. Dose to heart and lungs was significantly reduced, consequently reducing cumulative mortality risks, while still maintaining adequate target coverage.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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