Radiotherapy and Oncology 131 (2019) 174–178

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Validation of a robust strategy for proton spot scanning for oesophageal cancer in the presence of anatomical changes

Ditte Sloth Møller [a,*], Markus Alber [b], Marianne Nordsmark [c], Tine Bisballe Nyeng [a], Christina Maria Lutz [a], Lone Hoffmann [a]

[a] *Department of Medical Physics, Aarhus University Hospital, Denmark;* [b] *Department of Radiation Oncology, Heidelberg University Hospital, Germany;* [c] *Department of Oncology, Aarhus University Hospital, Denmark*

ARTICLE INFO

Article history:
Received 11 May 2018
Received in revised form 20 September 2018
Accepted 25 September 2018
Available online 16 October 2018

Keywords:
Oesophageal cancer
Adaptation
Anatomical changes
Proton therapy

ABSTRACT

SFUD strategies with one or two posterior proton beams and three target coverage strategies are compared with IMRT and tested for robustness towards anatomical changes by recalculation on surveillance CTs during treatment. We find posterior beam SFUD combining PTV coverage with robust optimization increases robustness towards anatomical changes compared to IMRT.

The current standard treatment for oesophageal cancer patients is concomitant chemotherapy and radiotherapy (RT) [1], if possible followed by surgery [2], irradiating large parts of lungs and heart causing toxicity [3,4]. Dose to these organs at risk (OARs) can be reduced using proton therapy (PT) [5–8]. The hypothesis that dose reduction translates to reduced complication rates is supported by several small non-randomized studies showing lower cardiac and pulmonary complication rates for PT [9–13].

While the planned dose of PT is promising, dose deterioration due to respiration and interfractional anatomical changes could undermine the potential benefit. Anatomical changes can be large and the dosimetric impact has not been quantified. The changes include interfractional diaphragm baseline shifts [14,15], mediastinal deformation [14,15] and gastric filling [16]. Since proton dose distributions are more sensitive to density changes due to their finite range [17,18], the dose deterioration could be more severe, making PT treatment unacceptable due to high risk of underdosage. For simulated interfractional setup-errors, much smaller than the anatomical changes observed during RT [14–16], Warren et al. [6] found dose deterioration for PT.

The impact of respiration on the target motion is primarily observed in the inferior-superior direction and is on the mm scale [19]. It has been investigated in detail for lung cancer where larger respiratory amplitudes combined with large density changes between the target and the surrounding tissue increases the impact of respiration [20]. For oesophageal PT, choosing posterior beam angles can minimize target dose deviations due to respiratory motion by avoiding entrance through the diaphragm [21].

This study develops a single field uniform dose (SFUD) PT strategy with optimal use of field directions and robust optimization (RO) and validates it for real interfractional anatomical changes occurring during RT.

Material and methods

Patient data

This study includes 26 consecutive patients with central or distal oesophageal or gastro-oesophageal junction (GEJ) cancer (five central, six distal and 15 central/distal tumours). Pre-operative RT (41.4 Gy/23 fractions) [2] was administered to 22 patients. Definitive RT (50 Gy/25 fractions) was administered to 4 patients. Concomitant chemotherapy was administered in both groups. Carboplatin/paclitaxel in the pre-operative group and cisplatin/fluorouracil in the definitive group. For details on target definition and margins, see Supplementary.

* Corresponding author at: Aarhus University Hospital, Department of Medical Physics, Noerrebrogade 44, Building 5J, 2. Floor, 8000 Aarhus C, Denmark.
E-mail address: dittmoel@rm.dk (D.S. Møller).

https://doi.org/10.1016/j.radonc.2018.09.018
0167-8140/

IMRT planning and treatment

All patients were treated with 5–8 IMRT fields covering the PTV with a homogeneous dose (95–107%). Treatment planning was performed in Eclipse 11 (Varian Medical Systems) using the AAA algorithm and optimized to minimize OAR dose always complying with clinical constraints (see Supplementary).

Retrospective SFUD planning

Proton treatment plans were generated retrospectively in Eclipse 13.7 using a pencil beam algorithm. Energy layer spacing was fixed at 3.5 MeV and the spot size (σ) in air at isocentre was between 4 mm (240 MeV) and 6 mm (70 MeV). All PT plans were optimized with a SFUD algorithm complying with the same OAR constraints as the IMRT plans. SFUD was chosen because full Intensity Modulated Proton Therapy (IMPT) gave no significant decrease in OAR dose, while SFUD has been shown to improve robustness compared to full IMPT. To account for planning and treatment-related uncertainties, three target coverage strategies were investigated: Homogeneous coverage of the PTV as used in photon planning ($SFUD_{PTV}$), RO to the CTV while neglecting the PTV ($SFUD_{ROB}$) and finally RO to the CTV while covering the PTV ($SFUD_{PTVROB}$). RO accounted for 3 mm isocentre shifts and 3% density uncertainty. The RO was implemented using minimax in Eclipse 13.7 [22,23].

Two SFUD field configurations were tested. A single posterior-anterior (PA) field (1f-SFUD) and two oblique PA fields separated by 30 degrees (2f-SFUD). Only posterior beams were chosen to minimize dose deterioration due to respiration [21] combined with the hypothesis that they are more robust towards interfractional changes of the diaphragm. In total, six plans were optimized for all patients: 1f-$SFUD_{PTV}$, 1f-$SFUD_{ROB}$, 1f-$SFUD_{PTVROB}$, 2f-$SFUD_{PTV}$, 2f-$SFUD_{ROB}$, and 2f-$SFUD_{PTVROB}$. No objectives were put on OARs as all normal tissue constraints were readily fulfilled.

Impact of interfractional anatomical changes

For all patients, an additional surveillance CT-scan (s-CT) was acquired at approximately fraction 10 and used for recalculation of both IMRT and SFUD plans. Target and all OARs were re-delineated on all sCTs by an experienced radiation oncologist. The percentage of the CTV receiving 95% of the prescribed dose ($V_{95\%}$) and the dose to OARs were compared for all plans between pCT and sCT and used as a measure of plan robustness towards anatomical changes. All anatomical changes observed between pCT and sCT were found to be systematic as they also appeared on the daily CBCT-scans for at least three consecutive fractions (see Supplementary). The dose calculated on sCT can therefore be used as a surrogate for persistent dose deterioration during RT.

Results

For all SFUD and IMRT plans at least 99.5% of the CTV volume was covered with 95% of the dose for all patients. Dose to all OARs except skin were significantly lower for the SFUD plans compared to the IMRT plans (see Supplementary). For the SFUD planning strategies, 1f- and 2f-SFUD plans delivered nearly identical doses to heart and liver, while the dose to lungs and kidneys was slightly larger for the 2f-SFUD plans. For both 1f- and 2f-SFUD plans, the three optimization strategies resulted only in small differences in OAR doses.

The 26 patients were divided into groups based on a visual comparison of pCT and sCT. Deformations of the CTV or mediastinum above 5 mm and diaphragm baseline shifts above 10 mm on sCT were noted as anatomical changes. For the diaphragm baseline shift seen on sCT, it was verified by comparison of the p4D-CT and the s4D-CT that the observed change was due to a shift in the mean position of the diaphragm and not a change in the respiratory motion pattern. Three groups were made based on interfractional changes:

- Group A: Patients without anatomical changes (13 pts).
- Group B: Patients experiencing deformations of the mediastinum and target (7 pts).
- Group C: Patients experiencing changes in the diaphragm position combined with target deformations and eventually mediastinal deformations (6 pts).

For group A, recalculation of IMRT and all SFUD plans on sCT resulted in $V95\%_{CTV} > 99.5\%$ maintaining full target coverage. For group B, under-dosage of the CTV was observed, see box plot in Fig. 1 (panel a). The multi-field IMRT plans handled target deformation quite well maintaining $V95\%_{CTV} > 98.3\%$ for all patients. The robustness of SFUD plans depended on the number of fields and optimization strategy. For the patient with the largest decrease in target overage, the $V95\%_{CTV}$ dropped to between 93.4% (1f-$SFUD_{ROB}$) and 97.9% (2f-$SFUD_{PTVROB}$). For the remaining six patients in the group, $V95\%_{CTV}$ exceeded 95% for all patients in all SFUD plans (data underlying Fig. 1). In group B, 2f-SFUD was slightly more robust than 1f-SFUD, while no difference was seen for group C. However, the three SFUD optimization strategies affect robustness. For SFUD plans robustly optimized to CTV and covering PTV ($SFUD_{PTVROB}$), target coverage was almost as good as for IMRT, maintaining $V95\%_{CTV} > 97.9\%$ for all patients. On the contrary, SFUD plans robust optimized to the CTV but discarding the PTV, had the largest decreases in $V95\%_{CTV}$, both in median dose decrease and outliers.

For patients with diaphragm-position changes and target deformations (group C) more severe under-dosage was observed for IMRT plans. A box plot for this group is displayed in Fig. 1, panel b. For all patients in group C, the decrease in coverage was larger for the IMRT plan than for the SFUD plans. For one patient, recalculation of the IMRT plan on s-CT yielded a $V95\%_{CTV}$ coverage as low as 65.3%. In this patient, the diaphragm baseline moved 1.7 cm cranially and target deformations were seen as shown in Fig. 2. The SFUD showed only slight under-dosage. For the SFUD plans, the maximum decrease in $V95\%_{CTV}$ ranged from 88.8% (1f-$SFUD_{ROB}$) to 92.7 (2f-$SFUD_{PTV}$). Assuming a threshold of $V95\%_{CTV} > 98\%$, only one of the IMRT plans fulfilled this requirement, while all but one 2f-$SFUD_{PTVROB}$ plans did. As for group B, comparison of the SFUD plans in terms of robustness showed no difference between one- and two-posterior-field plans, while $SFUD_{PTVROB}$ plans seem more robust than the other target coverage strategies.

Discussion

The current study illustrates the impact of beam angle selection on SFUD plan robustness. Anatomical changes occured in 50% of the patients and were separated in two groups. For Group B patients, experiencing deformation of the mediastinum and target, only small decreases in target coverage were observed. For group C patients, experiencing changes in diaphragm position as well as target deformation, larger decrease in target coverage was observed, especially for IMRT. All but one IMRT plan would have required replanning (assumed adaption threshold $V95\%_{CTV} > 98\%$), while this would only be necessary for one of the patients if the 2f-$SFUD_{PTVROB}$ plan was chosen. These results could be explained by the posterior beam arrangement, which avoids entrance through the diaphragm and is therefore not as susceptible to diaphragmatic positional changes as a 5–8 beam IMRT plan. Further, our findings substantiate the results by Zeng et al. [13],

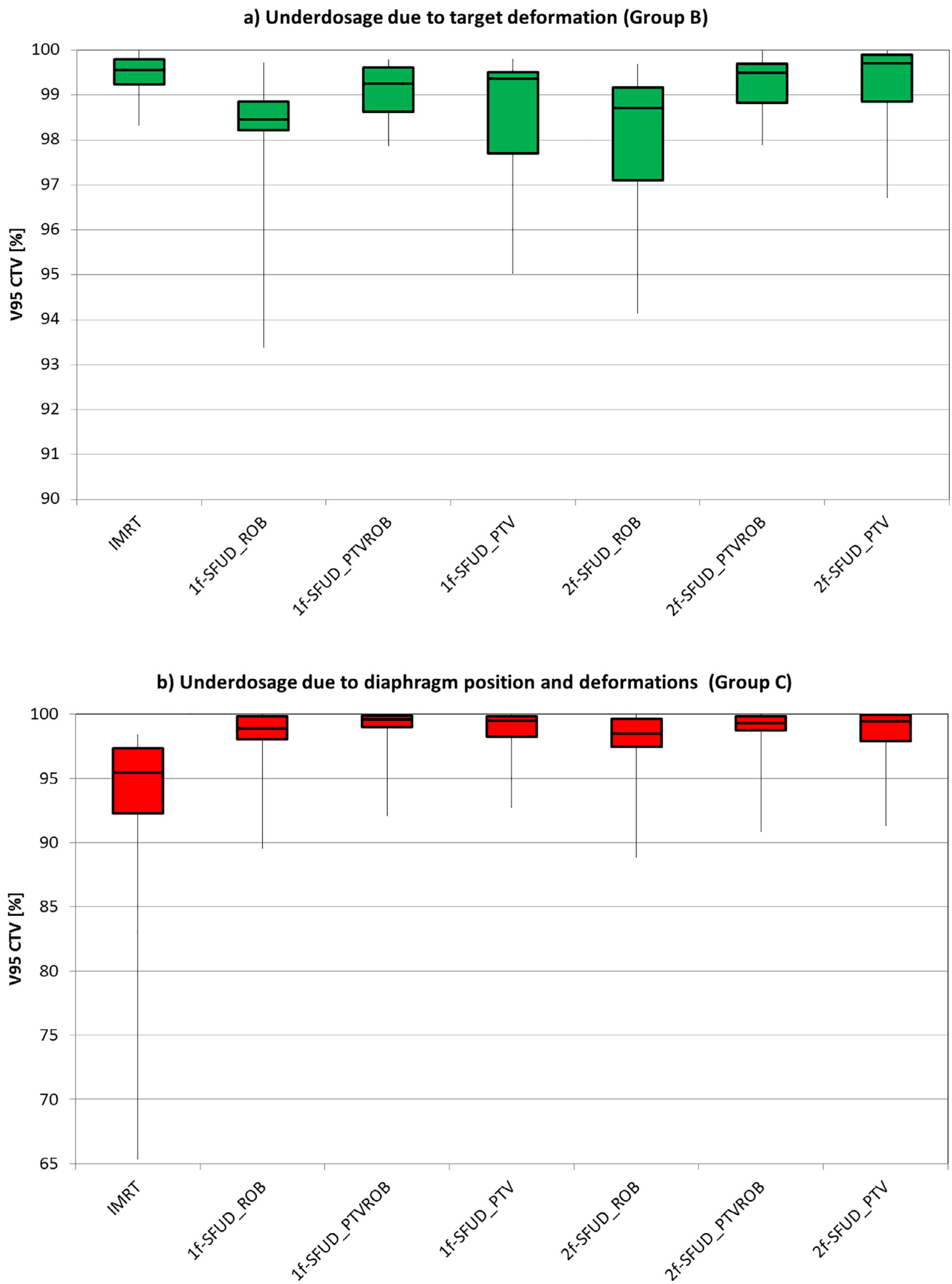

Fig. 1. Boxplot of the CTV coverage for IMRT and SFUD plans for all patients in group B (a) and group C (b). The box shows the range between 1st and 3rd inter quartile ranges, the vertical line in the middle indicates the median value and the whiskers range from minimum to maximum value. Note the change in scale between the two plots.

who reported that none of their 13 SFUD patients required adaptation. However, the criteria used to make this judgment were not reported and can thus not be compared. It is important to note that the change in diaphragm position is not due to a change in respiratory motion, but a real systematic interfractional deviation in the position of the diaphragm. As shown by Jin et al. the

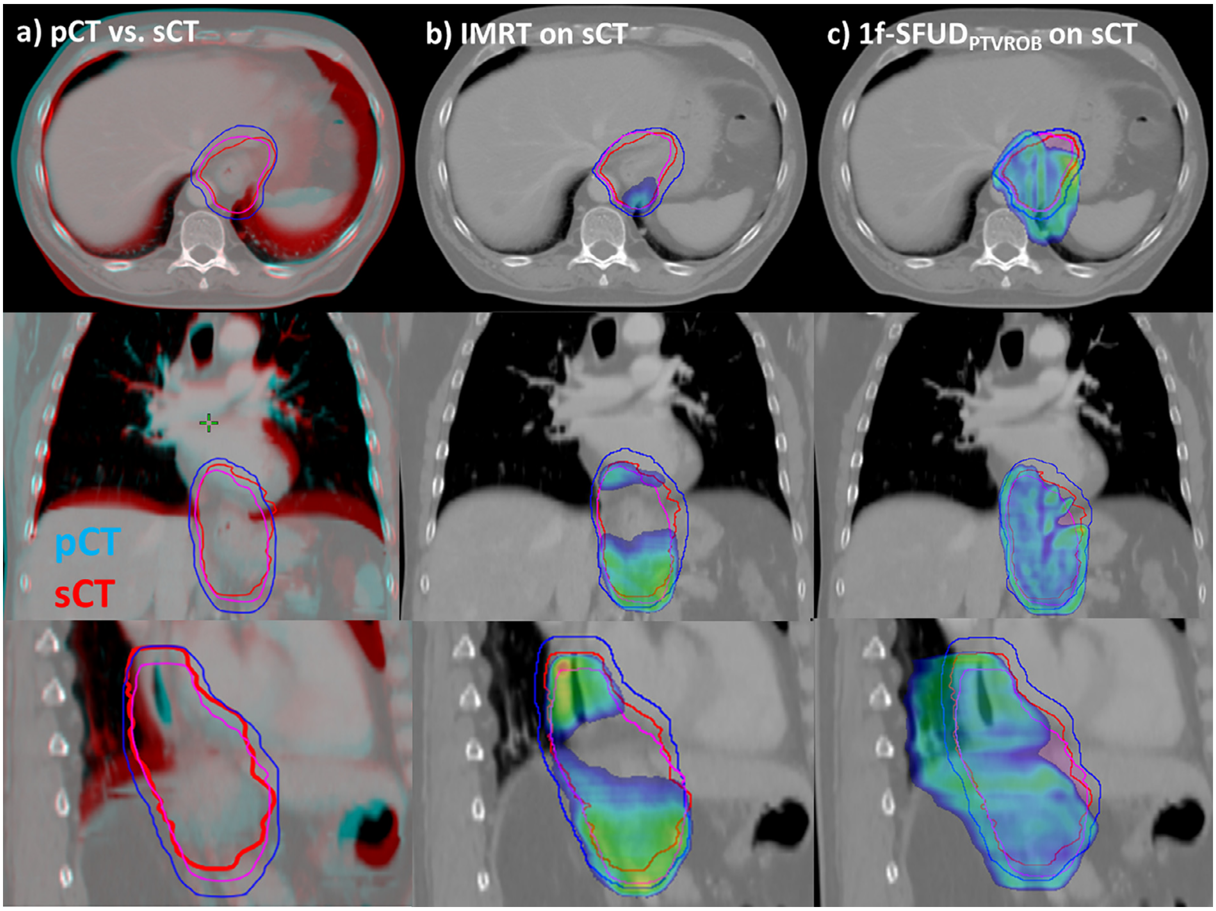

Fig. 2. Example of patient with anatomical changes. (a) Overlay of pCT and sCT with the diaphragm moved more cranially on the sCT. The CTV delineated on the pCT (pink) and the associated PTV (blue) is shown. The CTV on the sCT is shown in red. (b) Recalculation of IMRT on sCT: Dose distribution in dose colorwash for doses above 95% of the prescribed dose. (c) Recalculation of 1f-$SFUD_{PTVROB}$ on sCT: Dose distribution in dose colorwash for doses above 95% of the prescribed dose. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

interfractional variability of the respiratory amplitude and trajectory is limited, while interfractional shifts can be large [24]. Warren et al. evaluated the robustness of SFUD plans for a three beam arrangement (two lateral oblique and one anterior) for rigid setup-errors. They found a higher risk of target under-dosage for SFUD than VMAT [6]. This is opposite to the findings in the current study, and may be explained by the beam arrangement rather than the use of real anatomical changes in our study compared to rigid setup-errors in the study by Warren et al. [6]. In order to test this hypothesis, SFUD plans with one posterior and one lateral beam were created for selected patients (data not shown) and recalculated on the sCT. For this beam arrangement, the robustness for anatomical changes was worse than or similar to IMRT plans. Thus, the current study illustrates the importance of beam angle selection on plan robustness to anatomical changes.

With reference to the current discussion/trend to discard the PTV concept for PT, RO including rigid setup-errors and density uncertainty was tested. When the PTV was discarded and RO to the CTV solely used ($SFUD_{ROB}$), robustness towards anatomical changes decreased compared to the combination of a PTV with RO ($SFUD_{PTVROB}$). Since only rigid shifts are implemented in the applied RO, it is reasonable to assume that this difference is caused by the anatomical deformations. Including also this type of uncertainty into RO could improve the robustness of PT even further. In this study we found that $SFUD_{PTVROB}$ plans required minimal replanning compared to the other planning strategies. This demonstrates that the impact of anatomical deformations can be compensated sufficiently by a margin. The normal tissue toxicity is rather similar between the $SFUD_{ROB}$ and $SFUD_{PTVROB}$ plans, showing only minor increased dose for $SFUD_{PTVROB}$. Our results suggest, that the optimal RO strategy should include either realistic deformations or a combination of margins and RO to account for the deformations frequently observed in oesophageal cancer.

The current study investigated the uncertainties introduced by interfractional changes during treatment of oesophageal tumours. Before clinical introduction, full evaluation of the uncertainties in planning and delivering SFUD should be performed. In this study we did not consider the effect of respiratory motion but compared doses between the midventilation phase of pCT and sCT to find the effect of interfractional anatomical changes. The respiratory motion of the GTV-T was in mean (SD) 2(1)mm left–right and anterior-posterior, and 6(2) mm inferior-superior in concordance with the results from Jin et al. [24], where respiratory motion of fiducial markers were measured for 24 patients. As for the interfractional changes the dose deterioration due to respiration is highly dependent on the field directions. Yu et al. investigated dose deterioration for varying IMPT field directions and found that it was minimal for posterior beams due to avoidance of entrance through the diaphragm [21]. RO accounting for respiratory motion reduced the dose deterioration. For the patient with largest respiratory amplitude (10 mm inferior-superior) in the current study, $SFUD_{PTVROB}$ was recalculated on all phases of the 4D-CT revealing maintenance of $V95\%_{CTV}$ = 100% throughout the respiratory cycle. For lung cancer patients where the tumour is surrounded by low-density tissue and the respiratory amplitudes are generally larger, the dose deterioration observed is larger and different respiratory motion management strategies can be applied [7,20,25,26]. These techniques are not necessary for the vast majority of oesophageal cancer patients treated with posterior beams.

Comparison of PT and IMRT in terms of doses to OARs depends on field directions and target coverage strategies. In this study, SFUD plans were chosen to achieve optimal robustness towards anatomical changes, and compared to IMRT, SFUD reduced the mean heart dose to 54% and the mean lung dose to 28%, which is larger than most previous PT study findings [5, 6, 8, 13, Supplementary]. This shows that the conservative optimization strategy (SFUD with no dose constraint) meets the expectations of OAR sparing for PT.

In conclusion, robust SFUD plans with posterior field directions secured a high robustness towards anatomical changes. The best robustness was achieved with RO to the CTV in combination with a PTV. The robust SFUD plans maintain a significant sparing of dose to normal tissue compared to IMRT.

Acknowledgements

This research was supported by a grant from the Danish Cancer Society.

Conflict of interest statement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.09.018.

References

[1] So B, Marcu L, Olver I, Gowda R, Bezak E. Oesophageal cancer: which treatment is the easiest to swallow? A review of combined modality treatments for resectable carcinomas. Crit Rev Oncol Hematol 2017;113:135–50.
[2] Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS):long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090–8.
[3] Beukema JC, van Luijk P, Widder J, Langendijk JA, Muijs CT. Is cardiac toxicity a relevant issue in the radiation treatment of esophageal cancer? Radiother Oncol 2015;114:85–90.
[4] Morota M, Gomi K, Kozuka T, Chin K, Matsuura M, Oguchi M, et al. Late toxicity after definitive concurrent chemoradiotherapy for thoracic esophageal carcinoma. Int J Radiat Oncol Biol Phys 2009;75:122–8.
[5] Ling TC, Slater JM, Nookala P, Mifflin R, Grove R, Ly AM, et al. Analysis of intensity-modulated radiation therapy (IMRT), proton and 3D conformal radiotherapy (3D-CRT) for reducing perioperative cardiopulmonary complications in esophageal cancer patients. Cancers 2014;6:2356–68.
[6] Warren S, Partridge M, Bolsi A, Lomax AJ, Hurt C, Crosby T, et al. An analysis of plan robustness for esophageal tumors: comparing volumetric modulated arc therapy plans and spot scanning proton planning. Int J Radiat Oncol Biol Phys 2016;95:199–207.
[7] Zhang X, Zhao KL, Guerrero TM, McGuire SE, Yaremko B, Komaki R, et al. Four-dimensional computed tomography-based treatment planning for intensity-modulated radiation therapy and proton therapy for distal esophageal cancer. Int J Radiat Oncol Biol Phys 2007;72:278–87.
[8] Welsh J, Gomez D, Palmer MB, Riley BA, Mayankkumar AV, Komaki R, et al. Intensity-modulated proton therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumors: a dosimetric study. Int J Radiat Oncol Biol Phys 2011;81:1336–42.
[9] Makishima H, Ishikawa H, Terunuma T, Hashimoto T, Yamanashi K, Sekiguchi T, et al. Comparison of adverse effects of proton and X-ray chemoradiotherapy for esophageal cancer using an adaptive dose-volume histogram analysis. J Radiat Res 2015;56:568–76.
[10] Wang J, Wei C, Tucker SL, Myles B, Palmer M, Hofstetter WL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. Int J Radiat Oncol Biol Phys 2013;86:885–91.
[11] Lin SH, Komaki R, Liao Z, Wei C, Myles B, Guo X, et al. Proton beam therapy and concurrent chemotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys 2012;83:e345–51.
[12] Takada A, Nakamura T, Takayama K, Makita C, Suzuki M, Azami Y, et al. Preliminary treatment results of proton beam therapy with chemoradiotherapy for stage I–III esophageal cancer. Cancer Med 2016;5:506–15.
[13] Zeng YC, Vyas S, Dang Q, Schultz L, Bowen SR, Shankaran V, et al. Proton therapy posterior beam approach with pencil beam scanning for esophageal cancer: Clinical outcome, dosimetry, and feasibility. Strahlenther Onkol 2016;192:913–21.
[14] Nyeng TB, Nordsmark M, Hoffmann L. Dosimetric evaluation of anatomical changes during treatment to identify criteria for adaptive radiotherapy in oesophageal cancer patients. Acta Oncol 2015;54:1467–73.
[15] Yamashita H, Haga A, Hayakawa Y, Okuma K, Yoda K, Okano Y, et al. Patient setup error and day-to-day esophageal motion error analyzed by cone-beam computed tomography in radiation therapy. Acta Oncol 2010;49:485–90.
[16] Bouchard M, McAleer MF, Starkschall G. Impact of gastric filling on radiation dose delivered to gastroesophageal junction tumors. Int J Radiat Oncol Biol Phys 2010;77:292–300.
[17] De Reysscher D, Chang JY. Clinical controversies: photon therapy for thoracic tumors. Semin Radiat Oncol 2013;23:115–9.
[18] Engelsman M, Schwarz M. Physics controversies in proton therapy. Sem Rad Onc 2013;23:88–96.
[19] Jin P, Hulshof MC, de Jong R, van Hooft JE, Bel A, Alderliesten T, et al. Quantification of respiration-induced esophageal tumor motion using fiducial markers and four-dimensional computed tomography. Radiother Oncol 2016;118:492–7.
[20] Graeff C. Motion mitigation in scanned ion beam therapy through 4D-optimization. Phys Med 2014;30:570–7.
[21] Yu J, Zhang X, Liao L, Li H, Zhu R, Park PC, et al. Motion-robust intensity-modulated proton therapy for distal esophageal cancer. Med Phys 2016;43:1111–8.
[22] Park PC, Zhu XR, Lee AK, Sahoo N, Melancon AD, Zhang L, et al. A beam-specific planning target volume (PTV) design for proton therapy to account for setup and range uncertainties. Int J Radiat Oncol Biol Phys 2012;82:e329–36.
[23] Fredriksson A, Forsgren A, Hardemark B. Minimax optimization for handling range and setup uncertainties in proton therapy. Med Phys 2011;38:1672–84.
[24] Jin P et al. Interfractional variability of respiration-induced esophageal tumor motion quantified using fiducial markers and four-dimensional cone-beam computed tomography. Radiother Oncol 2017;124:147–54.
[25] Bert C, Saito N, Schmidt A, Chaudhri N, Schardt D, Rietzel E. Target motion tracking with a scanned particle beam. Med Phys 2007;34:4768–71.
[26] Furukawa T, Inaniwa T, Sato S, Shirai T, Mori S, Takeshita E, et al. Moving target irradiation with fast rescanning and gating in particle therapy. Med Phys 2010;37:4874–9.