Radiotherapy and Oncology 172 (2022) 32–41

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Treatment planning comparison in the PROTECT-trial randomising proton versus photon beam therapy in oesophageal cancer: Results from eight European centres

Lone Hoffmann [a,b,*], Hanna Mortensen [c], Muhammad Shamshad [a,b,c], Maaike Berbee [d], Nicola Bizzocchi [e], Rebecca Bütof [f,g], Richard Canters [d], Gilles Defraene [i], Mai Lykkegaard Ehmsen [c], Francesca Fiorini [h], Karin Haustermans [i,j], Ryan Hulley [m], Erik W. Korevaar [l], Matthew Clarke [m], Sebastian Makocki [f,g], Christina T. Muijs [l], Luke Murray [h], Owen Nicholas [k], Marianne Nordsmark [n], Ganesh Radhakrishna [m], Melissa Thomas [i,j], Esther G.C. Troost [f,g,o,p,q,r,s], Gloria Vilches-Freixas [d], Sabine Visser [l], Damien C. Weber [e,t], Ditte Sloth Møller [a,b]

[a] *Department of Medical Physics, Aarhus University Hospital;* [b] *Dept. of Clinical Medicine, Faculty of Health Sciences, Aarhus University;* [c] *Danish Center for Particle Therapy, Aarhus University Hospital, Denmark;* [d] *Department of Radiation Oncology (Maastro), GROW School for Oncology and Reproduction, Maastricht University Medical Centre+, The Netherlands;* [e] *Center for Proton Therapy, Paul Scherrer Institut, Villigen, Switzerland;* [f] *Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden;* [g] *OncoRay - National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden – Rossendorf, Germany;* [h] *Rutherford Cancer Centre, Shinfield, Reading, UK;* [i] *KU Leuven – University of Leuven - Department of Oncology – Laboratory of Experimental Radiotherapy;* [j] *University Hospitals Leuven, Department of Radiation Oncology, Belgium;* [k] *South West Wales Cancer Centre, Swansea University Board and Swansea University Medical School, UK;* [l] *Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, The Netherlands;* [m] *Christie Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, UK;* [n] *Department of Oncology, Aarhus University Hospital;* [o] *Institute of Radiooncology - OncoRay, Helmholtz-Zentrum Dresden-Rossendorf;* [p] *German Cancer Consortium (DKTK), Partner Site Dresden, and German Cancer Research Center (DKFZ);* [q] *National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany: German Cancer Research Center (DKFZ), Heidelberg;* [r] *Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden;* [s] *Helmholtz Association/Helmholtz-Zentrum Dresden - Rossendorf (HZDR), Dresden, Germany;* [t] *Radiation Oncology Department, University Hospital Zurich, Zurich, Switzerland*

ARTICLE INFO

Article history:
Received 9 January 2022
Received in revised form 6 April 2022
Accepted 28 April 2022
Available online 02 May 2022

Keywords:
Oesophageal cancer
Proton therapy
Intensity modulated radiotherapy
Treatment planning
Respiratory motion
Anatomical changes
Quality assurance
Phase III trial

ABSTRACT

Purpose: To compare dose distributions and robustness in treatment plans from eight European centres in preparation for the European randomized phase-III PROTECT-trial investigating the effect of proton therapy (PT) versus photon therapy (XT) for oesophageal cancer.

Materials and methods: All centres optimized one PT and one XT nominal plan using delineated 4DCT scans for four patients receiving 50.4 Gy (RBE) in 28 fractions. Target volume receiving 95% of prescribed dose ($V95\%_{iCTVtotal}$) should be >99%. Robustness towards setup, range, and respiration was evaluated. The plans were recalculated on a surveillance 4DCT (sCT) acquired at fraction ten and robustness evaluation was performed to evaluate the effect of respiration and inter-fractional anatomical changes.

Results: All PT and XT plans complied with $V95\%_{iCTVtotal}$ >99% for the nominal plan and $V95\%_{iCTVtotal}$ >97% for all respiratory and robustness scenarios. Lung and heart dose varied considerably between centres for both modalities. The difference in mean lung dose and mean heart dose between each pair of XT and PT plans was in median [range] 4.8 Gy [1.1;7.6] and 8.4 Gy [1.9;24.5], respectively. Patients B and C showed large inter-fractional anatomical changes on sCT. For patient B, the minimum $V95\%_{iCTVtotal}$ in the worst-case robustness scenario was 45% and 94% for XT and PT, respectively. For patient C, the minimum $V95\%_{iCTVtotal}$ was 57% and 72% for XT and PT, respectively. Patient A and D showed minor inter-fractional changes and the minimum $V95\%_{iCTVtotal}$ was >85%.

Conclusion: Large variability in dose to the lungs and heart was observed for both modalities. Inter-fractional anatomical changes led to larger target dose deterioration for XT than PT plans.

Cancer of the oesophagus and gastroesophageal-junction is the eighth most common cancer worldwide, with a high proportion of patients diagnosed at advanced stages [1,2]. Radiotherapy as part of tri-modality treatment is standard of care for locally-advanced

* Corresponding author at: Department of Medical Physics, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, entrance C, DK-8200 Aarhus N, Denmark.
E-mail address: Lone.Hoffmann@aarhus.rm.dk (L. Hoffmann).

https://doi.org/10.1016/j.radonc.2022.04.029
0167-8140/

oesophageal cancer patients [3,4]. Proton therapy (PT) may significantly reduce dose to organs at risk (OARs) compared to photon therapy (XT), while target dose remains similar [5–8]. Consequently, PT may result in reduced side effects [9–13] and potentially improved overall survival [14]. In a recent phase IIB randomized trial, the total toxicity burden (TTB), a composite score of eleven distinct adverse events, was compared between patients receiving PT and XT. The mean TTB was 2.3 times higher for XT than PT [10]. The upcoming European randomized phase III PROTECT-trial (PROton versus photon Therapy for Esophageal Cancer – a Trimodality strategy; NCT05055648) will further investigate the clinical effect of PT versus XT for oesophageal cancer patients treated with chemoradiotherapy followed by surgery.

Oesophageal cancer target volumes are generally large with complex shapes, and both position and shape of the tumour may change considerably between radiotherapy planning and delivery. Tumours are located in the mediastinum or upper abdomen in close proximity to radiosensitive OARs, such as spine, lungs and heart. Uncertainties during treatment delivery can potentially deteriorate the planned dose distribution, and strategies are necessary to ensure target coverage and avoid overdosage of OARs throughout the treatment course. Proton dose distributions are more sensitive to density changes due to the finite range of the proton beam [15], and anatomical changes can potentially severely impact the dose distribution during treatment compared to photon dose distributions. This may decrease the potential clinical benefit of the physical dose distribution for PT, when compared to XT and, if undetected and uncorrected, lead to decreased local control or increased radiation-induced adverse events. Intra-fractional variability is a result of respiratory and cardiac motion, which may result in positional changes during treatment delivery [16–19]. Inter-fractional variability is related to anatomical changes such as inter-fractional shifts of the diaphragm, tumour deformation and changes in gastric filling, which can cause large target under-dosage for both PT and XT [8,20]. For PT, posterior beam directions have been shown to reduce the dosimetric effect of anatomical changes and respiratory motion as entrance through the diaphragm is avoided [8,21,22]. The complexity in radiotherapy treatment of oesophageal cancer calls for strict quality assurance (QA) guidelines in order to secure optimal treatment delivery. Former studies have shown that the quality of treatment plans is correlated to e.g. patient local control or overall survival, pointing out that high standards for QA may influence the trial outcome [23,24]. In the European PROTECT-trial, strict QA-guidelines were developed for the trial to secure high-quality PT and XT plans.

The aim of the present study was to compare dose distributions and robustness in XT and PT treatment plans for oesophageal cancer patients, optimized at eight European centres in preparation of the PROTECT-trial. Differences in dose to OARs as well as target dose robustness towards respiratory motion, setup uncertainties and anatomical changes during the treatment course were investigated. All optimization and evaluation concepts were based on strict QA-guidelines within the trial.

Materials and methods

Patients, target definition and images

Anonymized four-dimensional computed tomography (4DCT) scans for four oesophageal cancer patients were distributed to eight European radiotherapy centres. The patients were selected from a cohort of patients treated at Aarhus University Hospital (AUH) (approved by the Danish Patient Safety Authority). The patients were chosen to ensure different location and extension of the primary tumours and included patients with (A) 11 cm long mid-oesophageal tumour with three tumour-near pathological lymph nodes and a total CTV volume of 321 cm^3, (B) 4 cm long upper-oesophageal tumour with two pathological lymph nodes cranial to the primary tumour and a total CTV volume of 119 cm^3, (C) 6 cm long gastro-oesophageal junction tumour with one intra-abdominal pathological lymph node and a total CTV volume of 252 cm^3, and (D) 2.5 cm long voluminous infra-diaphragmatic tumour extending into the stomach with four tumour-near pathological lymph nodes and a total CTV volume of 271 cm^3.All patients were deemed candidates for curative treatment consisting of surgery and pre-operative chemoradiotherapy and concomitant paclitaxel and carboplatin according to the CROSS-regimen [3]. All patients had available both a planning 4DCT (pCT) and a surveillance 4DCT (sCT) scan acquired at fraction ten. Two of the patients were selected based on the occurrence of large anatomical changes between pCT and sCT.

The gross tumour volumes for tumour and pathological lymph nodes were delineated centrally (AUH) and expanded to a clinical target volume (CTVtotal) according to the trial delineation guidelines [25]. The delineations were performed at the mid-ventilation (mv) scan and the average scan of pCT. Additionally, CTVtotal and spinal cord were deformably propagated (Eclipse, Varian Medical Systems) to all phases in the 4DCT scan, followed by a manual correction by an experienced oncologist (HM). CTVtotal on all phases was subsequently accumulated into iCTVtotal [26–27]. Target and OARs were delineated in a similar way on the sCT.

Treatment planning

All centres optimized one PT and one XT plan for each patient using the average- or mv-image of the pCT as the nominal scenario, see Table S1. Four centre-specific treatment planning systems were used, see Table S2. In the PROTECT-trial, the centres must choose between 41.4 Gy(relative biological effectiveness (RBE)) in 23 fractions and 50.4 Gy(RBE) in 28 fractions with RBE = 1.1 for PT. For this treatment planning study, 50.4 Gy(RBE) in 28 fractions was chosen. For the nominal XT and PT plans, the iCTVtotal volume receiving 95% of prescribed dose, $V95\%_{iCTVtotal}$ >99% was required. For the OARs, first priority constraints, being mandatory to fulfil, were set for lungs (mean lung dose (MLD) <20 Gy, V_{20Gy} <35% and V_{5Gy} <70%), spinal cord ($D_{0.05cm3}$ <45 Gy) and body ($D_{0.05cm3}$ <110%, D_{1cm3} <107%). Additionally, second priority constraints, which should be fulfilled if possible were set for heart, kidney, liver, bowel cavity, stomach, and spleen, see Table S3. Target coverage was prioritized higher than OAR dose except for spinal cord.

For PT plans, patients were required to be treated with pencil beam scanning technique using 2–3 beams. Only posterior beams (140–220 degrees) were allowed. Robust optimization (RO) taking rigid setup-errors and range uncertainties into account was mandatory. For RO, the planning iso-centre was required to be shifted at minimum in six different *x*, *y*, and *z* directions. Range-errors were included by applying a perturbation on the CT densities. The setup-errors used for the optimization should be based on the setup-errors determined at each clinic. The RO of iCTVtotal were allowed to be combined with coverage of the iCTVtotal expanded with a margin [8]. This strategy was used in three centres. Five centres used RO-only. The RO setup-errors used varied between 5–8 mm (Table S4).

For XT, VMAT or IMRT were required with no beam angle restrictions. Coverage of the planning target volume (PTV), created by adding a margin to the iCTVtotal based on setup-errors determined at each clinic was required. The PTV-margins varied between 5–8 mm.

Advanced dose calculation algorithms were mandatory for both modalities.

Robustness evaluation before treatment

Robustness towards centre-specific setup (3–8 mm) and range (density variation 3–5%) errors was evaluated on the average- or mv-image used for treatment planning (Table S4). The robustness was required to be evaluated by shifting the iso-centre in at least six different *x*, *y*, and *z* directions and was performed for minimum 12 and maximum 42 scenarios. However, due to technical hurdles in the treatment planning system, one centre could not perform robustness evaluation for XT and another centre could only evaluate setup-errors for XT resulting in 6 scenarios. For both modalities, all scenarios were required to fulfil constraints for the target ($V95\%_{iCTVtotal}$ >97%), spinal cord ($D_{0.05cm3}$ < 50 Gy), and body (D_{1cm3} < 110%, D_{5cm3} < 107%).

Impact of inter-fractional motion during treatment

To evaluate the effect of anatomical changes during the treatment course, the nominal XT and PT plans were recalculated on the sCT using the average- or mv-image (same choice as for the pCT). A rigid registration on the vertebral column was provided. The effect of residual setup-errors and range uncertainty on the iCTVtotal was evaluated using a combination of 2 mm setup-error and the range uncertainty value used for the nominal treatment plans. The small setup-error was chosen to simulate the residual errors originating from e.g. intra-fractional errors. This error does not include e.g. delineation and setup uncertainties. The plans were assessed against the following dosimetric parameters, target ($V95\%_{iCTVtotal}$ >97%), spinal cord ($D_{0.05cm3}$ < 50 Gy), and body (D_{1cm3} < 110, D_{5cm3} < 107%).

Impact of respiratory motion

Robustness towards respiration was evaluated by recalculating the plans with fixed monitor units on all delineated respiratory phases of pCT and sCT. The plans were assessed against $V95\%_{CTVtotal}$ >97% for all phases.

Statistics and NTCP estimation

Selected dose metrics were compared between plans. The statistical significance of any difference between dose to selected structures was assessed using the Wilcoxon signed-rank test. A

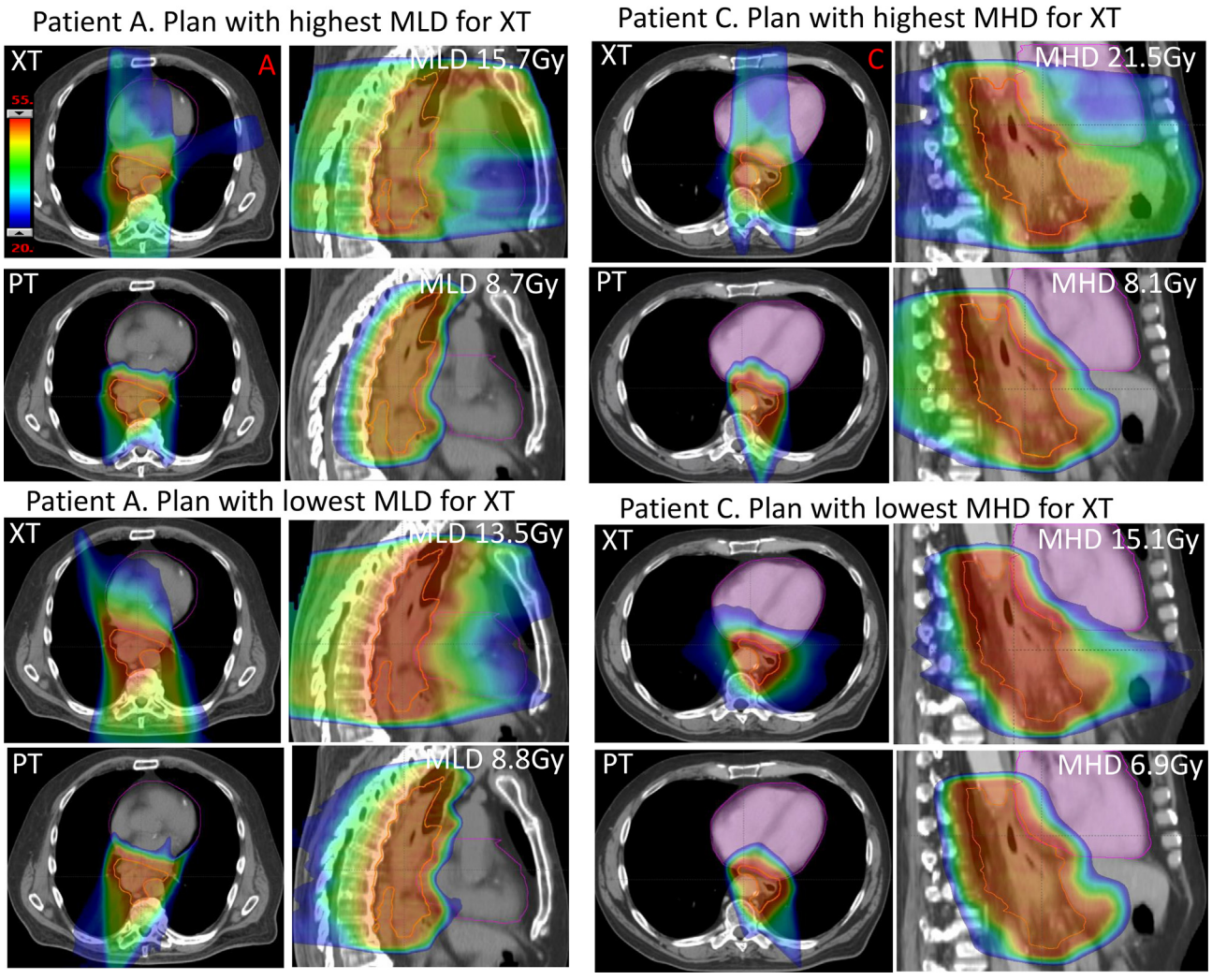

Fig. 1. Transversal and sagittal views for patient A and patient C. Doses above 20 Gy are shown with dose colour wash (scale shown as insert in upper left corner). iCTVtotal is shown in red. Heart is shown in translucent purple in patient C. Upper panels: XT and PT plan for the centre with highest MLD for XT (left) and highest MHD for XT (right). Lower panels: XT and PT plan for the centre with lowest MLD for XT (left) and lowest MHD for XT (right). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

p-value <0.05 was considered statistically significant. Correlation between selected dose metrics and PTV-margin, and technique for XT or setup-error used for RO and technique for PT was tested by determining the coefficient of determination from a linear regression. Similarly, correlation between plan robustness on sCT and technique, PTV margin, setup error, MLD, and MHD was investigated.

The risk of pulmonary complications was estimated using the NTCP model by Thomas et al. [28] based on histology, age and MLD for each of the XT and PT plans for all patients.

Results

A total of 8x2x4 = 64 plans were made. The first priority constraints MLD < 20 Gy and $V5Gy_{Lung}$ < 70%, were respected for all plans and for 62/64 plans, respectively. The second priority constraints, mean heart dose (MHD) < 26 Gy and $V30Gy_{Bowelcavity}$ < 300-cc were respected in 60/64 plans and all plans, respectively. All nominal plans met maximum constraints on spinal cord and body dose. The dose to lungs and heart varied considerably between centres for both XT and PT. In patient A, who received the highest MHD, variations between 20–32 Gy for XT and 5–12 Gy for PT was observed. Fig. 1 illustrates very different nominal dose distributions for two patients. For patient A, the plans from the two centres with highest and lowest MLD for XT are shown together with the PT plans from these centres. For patient C, the plans with highest and lowest MHD for XT are shown together with the PT plans from these centres. Dose metrics for each centre are given in Fig. S1.

Box plots of MLD, $V5Gy_{Lung}$, MHD and $V30Gy_{Bowelcavity}$ for the nominal plans at pCT illustrate the dosimetric variety for each of the patients (Fig. 2). All four dose-metrics were significantly lower for PT than XT. The median [range] differences in MLD, $V5Gy_{Lung}$, MHD and $V30Gy_{Bowelcavity}$ between each of the 32 centre-wise pairs of XT and PT plans were 4.8 Gy [1.1;7.6], 29.4% [0.7;47.9], 8.4 Gy [1.9;24.5], and 77.7 cc [1.8;352.3] (for bowel cavity, only patient C and D was evaluated), respectively (Fig. S2). The median pulmonary NTCP reduction with PT was 6.9% [1.4;23.5] using the model of Thomas et al. [28]. The ratio between MLD for XT and PT was 2.2 [1.2;4.8]. In this limited number of patients, no correlation was found between MLD and PTV-margin or technique for XT. Similarly, no correlation between MLD and RO setup-error or technique was found for PT. Likewise, for MHD no correlation was found (R^2 < 0.6).

For all nominal XT and PT plans, acceptable target coverage ($V95\%_{iCTVtotal}$ >99%) was reached. All plans met the constraints for robust evaluation in all except one scenario for target ($V95\%_{iCTVtotal}$ >97%), spinal cord ($D_{0.05cm3}$ < 50 Gy), and body (D_{1cm3} < 110%, D_{5cm3} < 107%) (Fig. 3a and Fig. S3a-c). Recalculation of the nominal treatment plan at all phases of the 4DCT met CTVtotal >97% (Fig. 3b + c).

Recalculation of treatment plans at sCT for all patients is illustrated in Fig. 3d for $V95\%_{iCTVtotal}$. The robustness evaluation was performed using density changes of 3.0–3.5% and 2 mm setup-errors. A substantial variability in robustness towards inter-fractional changes is seen between the patients and centres.

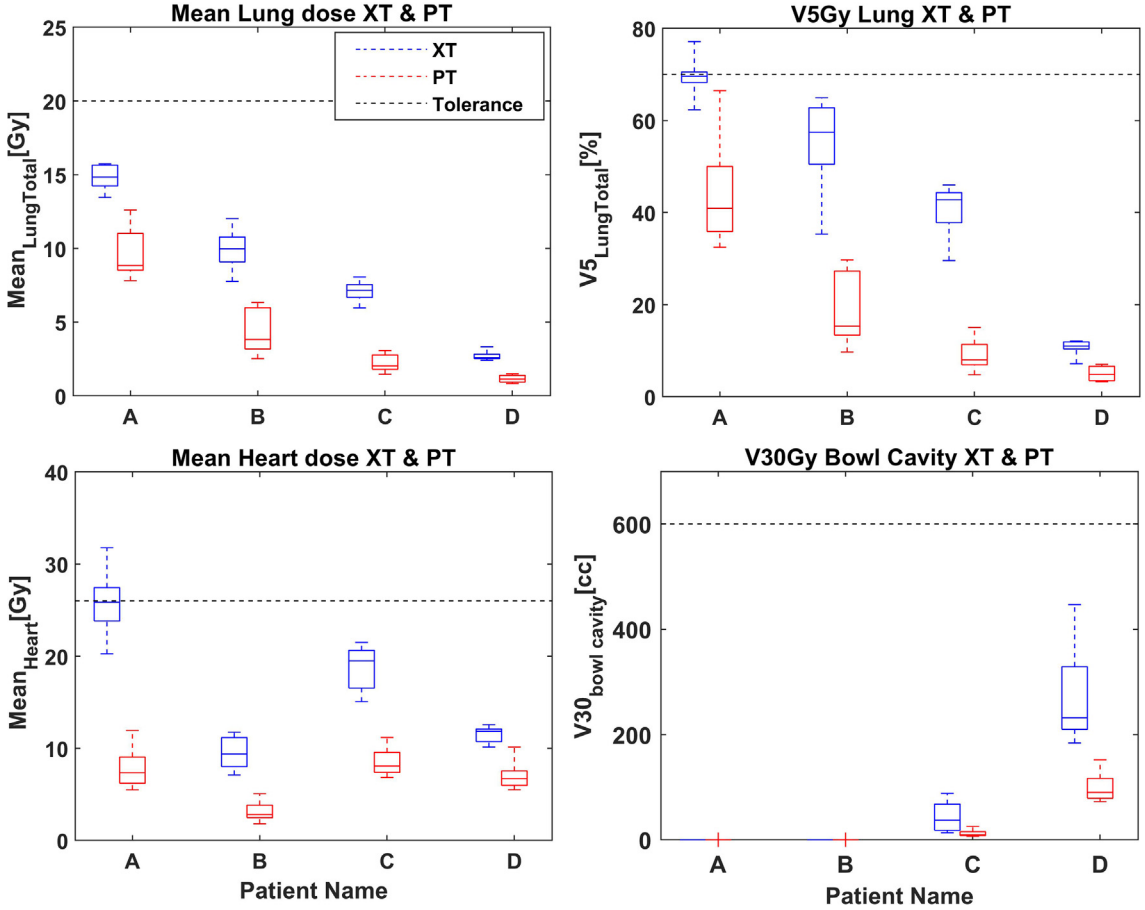

Fig. 2. Boxplots of MLD, $V5Gy_{Lung}$, MHD and $V45Gy_{Bowelcavity}$ for patient A–D. The boxplots illustrate median (horizontal line), 1st and 3rd interquartile ranges (box), and min/max (whiskers). Each box comprises nominal plans from all eight centres. XT plans are shown in blue and PT plans in red. The dotted lines show the tolerance level for each dose metric (lung dose metrics: first priority constraints; heart and bowel dose metrics: second priority constraints). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

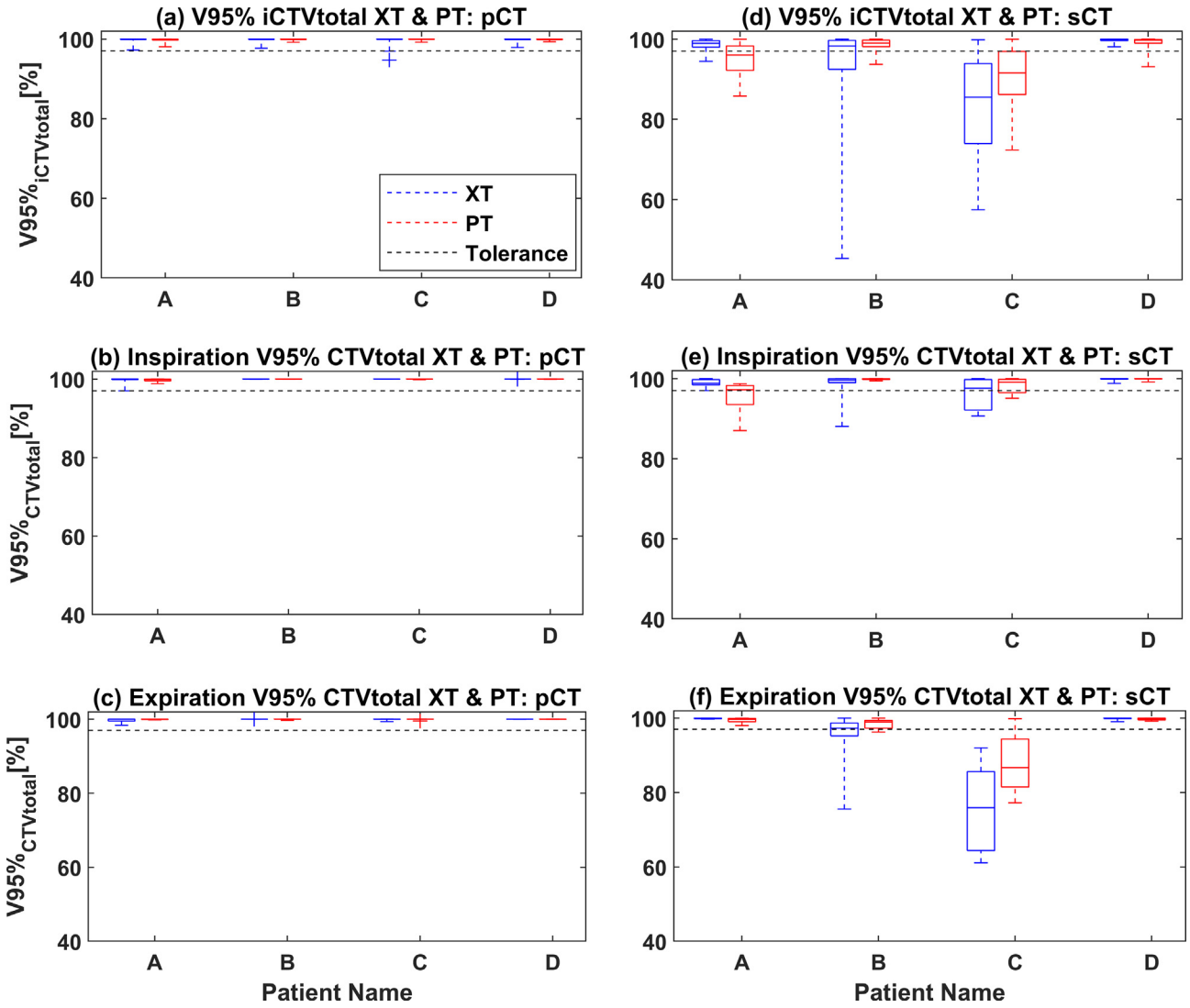

Fig. 3. Boxplots of iCTVtotal and CTVtotal for patients A–D. Left: pCT; right: sCT. Panels a,d: V95%$_{iCTVtotal}$. Each box comprises plans and robustness scenarios (setup and range) from all eight centres. Panels b,e: Nominal plan copied to inspiration phase, evaluation of V95%CTVtotal. Panels c,f: Nominal plan copied to expiration phase, evaluation of V95%CTVtotal. The boxplots illustrate median (horizontal line), 1st and 3rd interquartile ranges (box), and min/max (whiskers). XT plans are shown in blue and PT plans in red. The dotted lines show the tolerance level at 97%.

The centre-wise robustness evaluation on pCT and sCT is illustrated in Fig. 4 for patient B. In four PT centres, V95%$_{iCTVtotal}$ <97% and the minimum V95%$_{iCTVtotal}$ was 94% on sCT (Fig. 4b). In five XT centres, V95%$_{iCTVtotal}$ <97% and the minimum V95%$_{iCTVtotal}$ was 45% on sCT. In one centre, the median V95%$_{iCTVtotal}$ was higher for XT than PT. In patient B, the ventral part of the mediastinum was larger on sCT compared to pCT and a displacement of the target in the cranio-caudal direction occurred. These changes led to depletion of the target dose primarily for XT (Fig. 5). In order to minimize dose to the lungs, the XT dose was mostly delivered in the ventral-dorsal direction and thereby, the dose distribution was sensitive to the mediastinal changes. For the PT dose delivered by posterior beams solely, only the shift of the target in cranio-caudal direction influenced the dose (Fig. S4). The margins, setup errors, and delivery technique differed between the centres, leading to a difference in the sensitivity to anatomical changes. However, in this limited number of patients no correlation was found between the reduction in dose to iCTVtotal and delivery technique, PTV-margin, RO setup-error, MLD, or MHD for neither XT nor PT (R^2 < 0.5). The largest effect of the respiratory motion occurred for maximum expiration, where a shift of the target in the cranio-caudal direction occurred.

The centre-wise robustness evaluation for patient C is shown in Fig. 6. In all treatment plans but one, V95%$_{iCTVtotal}$ <97% and the minimum V95%$_{iCTVtotal}$ was 57% and 72% for XT and PT on sCT, respectively. The diaphragm shifted by 1.7 cm in cranial direction at sCT. This resulted in large target under-dosage, especially for XT where dose was delivered through the diaphragm (Fig. S5). Additionally, target shift and deformation were seen, leading to deterioration of the target dose for both modalities.

For patient A, the minimum V95%$_{iCTVtotal}$ for XT and PT was 95% and 85% on sCT, respectively. Under-dosage appeared in three and six plans for XT and PT, respectively. The diaphragm was shifted by 2.0 cm in the caudal direction at sCT and the distal part of the iCTVtotal was shifted by 1.0 cm (Figs. S6 + S7). For patient D, the minimum XT and PT dose was 98% and 93%, respectively. Only minor anatomical changes occurred at sCT (Figs. S8 + S9).

For all patients, target under-dosage on sCT due to respiratory motion was comparable to the worst-case scenario robustness evaluation.

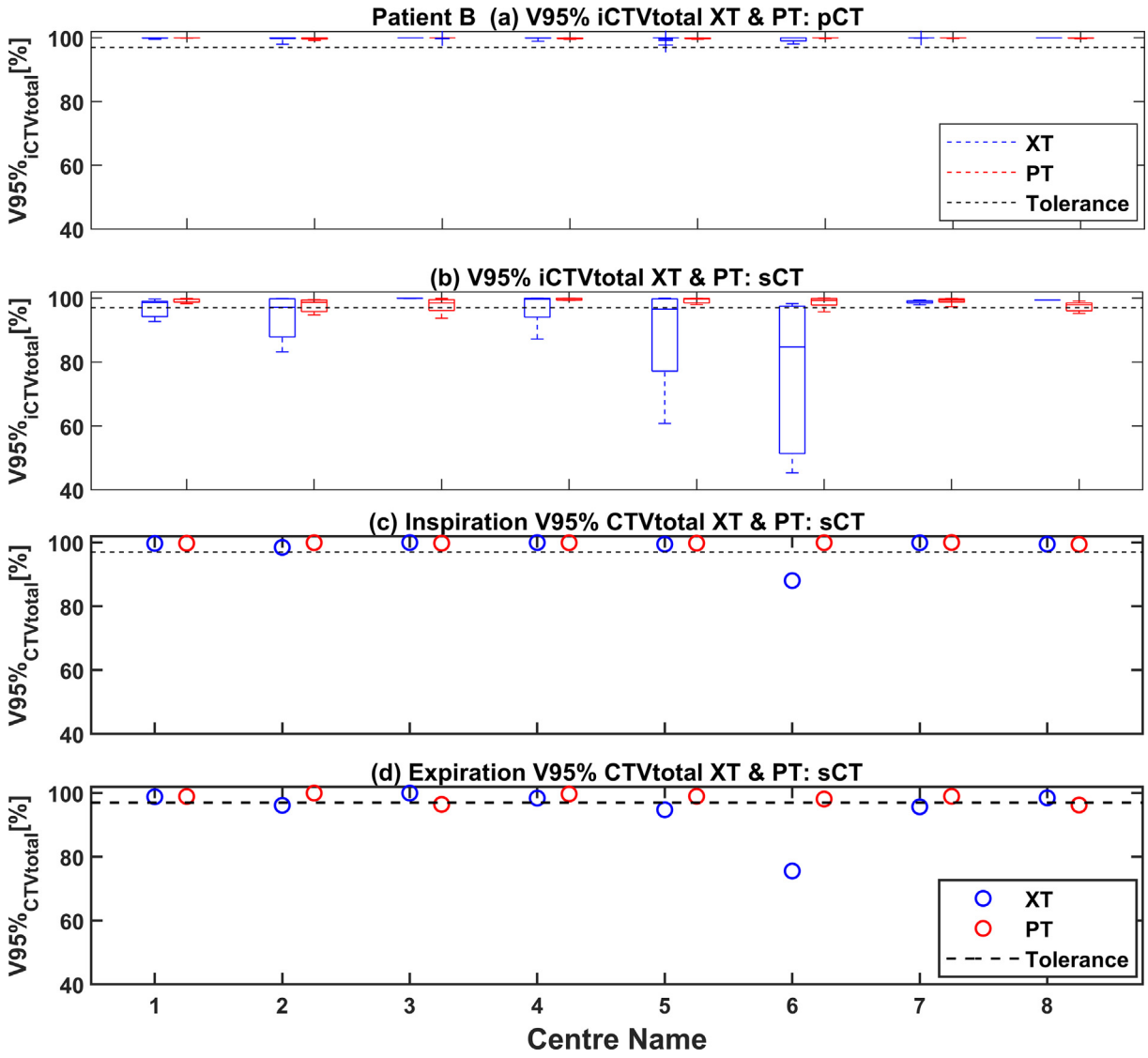

Fig. 4. Centre-wise robustness evaluation on pCT and sCT for patient B. The boxplots illustrate median (horizontal line), 1st and 3rd interquartile ranges (box), and min/max (whiskers). XT plans are shown in blue and PT plans in red. The dotted lines show the tolerance level at 97%. Panels a + b: The boxplots show coverage of the iCTVtotal at pCT and sCT at each one of the eight centres. The boxplot comprises nominal plan and robustness evaluation accounting for setup and range uncertainty. Note: In centre 8, no robustness evaluation was performed for XT. Panels c + d: Nominal plan recalculated on inspiration and expiration phase at sCT, evaluation of CTVtotal.

Robustness evaluation was performed at sCT for spinal cord ($D_{0.05cm3}$ < 50 Gy) and body (D_{1cm3} < 110%, D_{5cm3} < 107%). In all plans except one for patient A, the constraint for spinal cord was respected. For the body, overdosage was observed: D_{5cm3} >107% in six plans and D_{1cm3} >110% in one plan (Fig. S3d-e).

Discussion

In the present study, PT and XT plans were compared between eight European centres as part of the QA-process for the tri-modality PROTECT-trial. Compliance with strict QA-guidelines being mandatory for trial participation were investigated. A similar study has been performed for target delineation in the PROTECT-trial, showing good compliance with the guidelines [25].

Tri-modality treatment comes at a cost of considerable side-effects [11,29,30]. Serious acute and post-operative pulmonary and gastrointestinal complications are seen after thoracic radiotherapy [12,13,29]. In a former study on 444 patients, a strong association between MLD and pulmonary complications was shown [13]. Therefore, strict constraints and minimization of radiation dose to the lungs are important.

In the PROTECT-trial, the difference in pulmonary complications between the trial arms is expected to be primarily driven by post-operative complications. The complications were estimated from a NTCP model using MLD as the primary dose-metric [28]. An expected MLD-ratio between XT and PT of 2.75 was used for sample-size calculation in the PROTECT-trial. This corresponds to an estimated change in post-operative complications from 25% to 13%. In this in-silico study with only four patients, a ratio of 2.2 [1.2;4.8] was found. However, the centre-wise variability in MLD-ratio between the arms seen in this pre-treatment QA study, clearly shows that surveillance of the MLD-ratio during the trial inclusion period is required. All treatment plans will be collected continuously and the MLD-ratio will be monitored in order to update patient number if the MLD-ratio changes. Centre-wise differences in dose to OAR may go undetected in clinical trials unless specifically investigated. For instance, in the RTOG0617-trial, post-trial analysis showed that less toxicity occurred in patients treated with IMRT compared to conventional treatment [31]. Performing

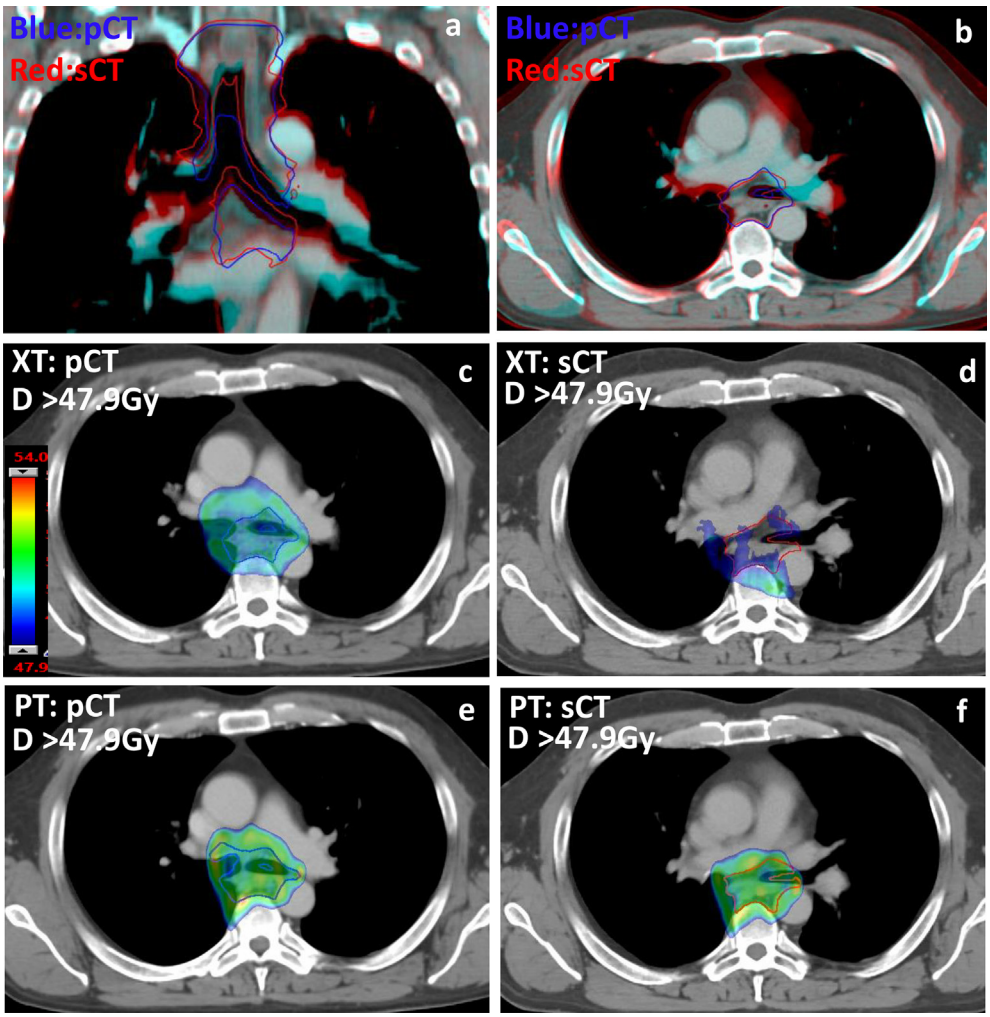

Fig. 5. CT images, delineations and dose distributions for patient B. iCTVtotal is depicted in blue (pCT) and red (sCT). Panels a + b: Frontal and transversal overlay of pCT (red) and sCT (turquoise) mv-images illustrating a shift in cranial direction and changes in mediastinal anatomy at sCT. Panels c + d: Doses above 47.9 Gy (95% of prescription dose) are shown for one centre with dose colour wash for the XT plan at pCT (c) and sCT (d). Panels e + f: Doses above 47.9 Gy (95% of prescription dose) are shown for one centre with dose colour wash for the PT plan at pCT (e) and sCT (f). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pre-trail QA, clarifies these differences prior to patient inclusion even though no conclusion on the MLD-ratio obtained during trial inclusion can be drawn.

Increased risk of heart toxicity has formerly been shown to be associated with chemotherapy and MHD [29,32–35], pointing out the importance of reducing heart dose. In this study, 60/64 plans complied with the MHD constraint. A significant reduction in MHD was found when applying PT compared to XT in agreement with former findings [12].

A huge variability in dose to the lungs and heart was seen between centres for both modalities even though restricted beam angles were required for PT. In the very limited number of patients for this study, no correlation between selection of margins, setup-errors, or treatment technique was seen. Variability in treatment planning may result from differences in optimization strategy and prioritization of dose to the OARs. Former inter-institutional treatment planning studies have shown a high degree of variability in treatment planning depending on human skills and resources [36,37]. No statistically significant difference between the systems applied, technique, number of beam angles, or education of the planner was found [36,37]. Knowledge-based planning has been shown to result in reduced dose to the OAR[38–41] and more standardized treatment plans[38,42–43] independently of technique, margins, and beam angles. Hereby indicating, that part of the variability is related to planner-individual decisions. In the PROTECT-trial, higher uniformity in treatment planning between centres will be obtained by feed-back on pre-trial treatment plans based on the current study, individual case review of every fifth patient, on-site visits, and yearly QA-workshops. An inter-disciplinary QA-group with participation from multiple centres will conduct the trial-QA. Additionally, for all treatment plans in the PROTECT-trial a RapidPlan model will be used to investigate if the dose to OAR can be substantially lowered.

Treatment planning studies may shed light on centre-wise differences and lead to optimized planning strategies and increased uniformity[44,45]. Results from treatment plan QA in the STAR-TReC trial showed huge variability in dose to OARs and a potential for more coherence between centres by discussion of the results on trial meetings[44]. In former studies reporting on pre-trial QA in multi-centre settings, one to five patients have been sent to the centres participating in the trial[44–47]. Based on the findings extracted from the centre-wise delineations and treatment plans, feedback was given to the centres leading to improved trial quality[44,46–47]. In the present study, four patients were submitted to eight centres. For pre-trial QA, the workload on the participating centres is very important and the number of patients need to be

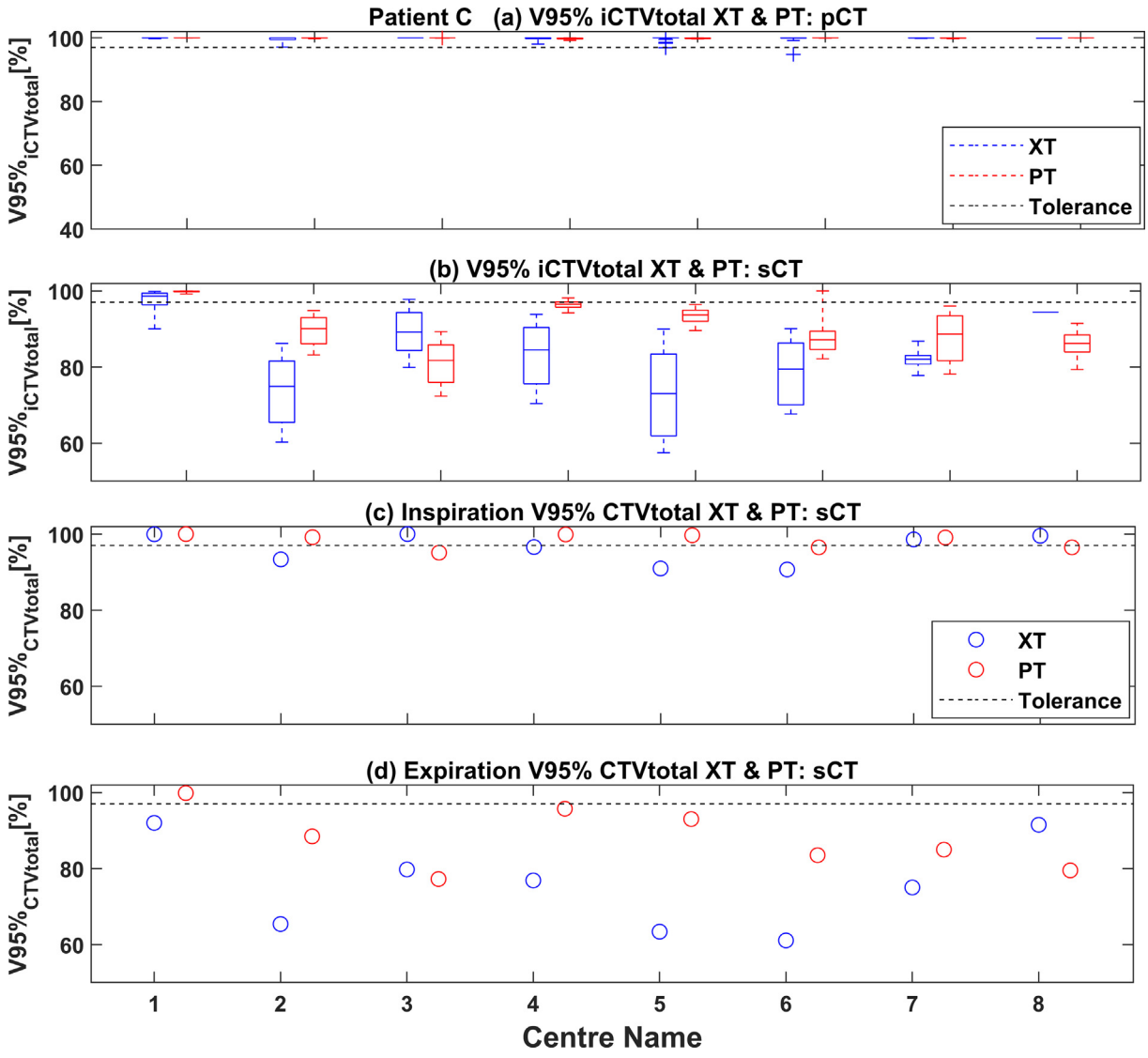

Fig. 6. Centre-wise robustness evaluation on pCT and sCT for patient C. The boxplots illustrate median (horizontal line), 1st and 3rd interquartile ranges (box), and min/max (whiskers). XT plans are shown in blue and PT plans in red. The dotted lines show the tolerance level at 97%. Panels a + b: The boxplots show coverage of the iCTVtotal at pCT and sCT (a + b) at each one of the eight centres. The boxplot comprises nominal plan and robustness evaluation accounting for setup and range uncertainty. Note: In centre 8, no robustness evaluation was performed for XT. Panels c + d: Nominal plan recalculated on inspiration and expiration phase at sCT, evaluation of coverage of CTVtotal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

kept fairly low in order for the centres to accommodate the workload. For the PROTECT-trial, we have chosen to include four patients with different tumour location and size, representing the variety of patients expected to be included in the trial.

Oesophageal cancer targets are prone to intra- and inter-fractional changes during radiotherapy treatment. Respiratory motion and setup-errors can partly be taken into account during treatment planning through margins and RO[16–19,21,48–49]. In this study, the effect of respiratory motion was evaluated by recalculation of the treatment plan at all phases of the 4DCT scans at pCT and sCT. The largest effect was seen in patient C showing intra-fractional motion of the diaphragm at sCT of 1.6 cm. The motion primarily influenced the XT plans, as only posterior beams, not passing through the diaphragm, were allowed for PT in agreement with former results[21–22].

Anatomical changes such as inter-fractional shifts of the diaphragm, tumour deformation, and changes in gastric filling or breathing pattern are difficult to predict and can cause large target under-dosage for both PT and XT[8,20]. The inter-fractional variation was most pronounced in the cranio-caudal direction in agreement with other studies[8,17,19]. Posterior beam directions for PT have been shown to reduce the effect of anatomical changes as entrance through the diaphragm and bowel is avoided[20–21]. This was indeed the case for patient C, where larger under-dosage was seen for XT compared to PT. However, PT was more prone to changes in patient positioning, as seen in patient A. Here, the patient's back was positioned slightly differently and the target was shifted ventrally, leading to larger under-dosage for PT than XT.

In all patients, huge variability in the target coverage at sCT was seen depending on the centre-specific treatment plan. Thus, the number of adaptations required will depend on the specific treatment plan including the centre-specific choice of PTV-margin or setup-error used for treatment planning. In this study, no correlation was found between the target coverage at sCT and treatment technique, or margin/setup-error strategy, or MLD, or MHD and larger studies are warranted to optimise robustness of both XT and PT plans. The variability may stem from differences in opti-

mization strategy which cannot be resolved based on the limited number of patients in this study. In the prospective PROTECT-trial enrolling 396 oesophageal cancer patients at thirty European XT and PT centres, plan robustness towards anatomical changes and respiratory motion will be evaluated on weekly CT scans being mandatory to acquire and evaluate for all centres. All data will be prospectively uploaded to a database and used for analysis of e.g. number of plan adaptations. The findings will be supplied to the centres through direct centre-specific feedback and yearly generalized feedback. The outcome will provide an extensive data set on correlation between plan robustness and treatment planning and delivery. According to the guidelines, the centre-wise PTV margins and setup-errors used for optimization should be based on setup-errors determined at each clinic. The margin and setup errors used varied between 5–8 mm and reflected the margins to be used in the prospective trial.

The strict QA-guidelines for the PROTECT-trial will impact the quality of European radiotherapy for oesophageal cancer by requiring all participating centres to improve their current methods. Treatment of oesophageal cancer is technically challenging due to a combination of respiratory motion and anatomical changes altering the position and shape of both target and OARs. Robust treatment planning, extensive 4D-imaging during the treatment course and adaptation of the treatment plan due to anatomical changes are mandatory to ensure full target coverage for all trial patients.

In conclusion, treatment planning and robustness evaluation for the European randomized phase III PROTECT-trial were evaluated in eight centres. Despite all centres meeting the first priority constraints for the nominal treatment plans, large variability in dose to OARs as well as plan robustness towards anatomical changes was found. Anatomical changes during the treatment course led to target dose deterioration. XT plans were less robust towards diaphragmatic motion than PT plans.

Acknowledgements

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 101008134. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. LH, MS and MN has received funding from Novo Nordisk Foundation grant No NNF19OC0057405, Denmark. GD is postdoctoral fellow of the Research Foundation Flanders (FWO, project 1292021N), Belgium.

Conflicts of interest

No.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.04.029.

References

[1] Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015. JAMA Oncol 2017;3:524–48.
[2] Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015;64:381–7.
[3] van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, Henegouwen MIVB, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074–84.
[4] Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. ESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v50–7.
[5] 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.
[6] Hirano Y, Onozawa M, Hojo H, Motegi A, Zenda S, Hotta K, et al. Dosimetric comparison between proton beam therapy and photon radiation therapy for locally advanced esophageal squamous cell carcinoma. Radiat Oncol 2018;13:23.
[7] Liao Z, Gandhi SJ, Lin SH, Bradley J. Does proton therapy offer demonstrable clinical advantages for treating thoracic tumors? Semin Radiat Oncol 2018;28:114–24.
[8] Møller DS, Alber M, Nordsmark M, Nyeng TB, Lutz CM, Hoffmann L. Validation of a robust strategy for proton spot scanning for oesophageal cancer in the presence of anatomical changes. Radiother Oncol 2019;131:174–8.
[9] Hurmuzlu M, Aarstad HJ, Aarstad AK, Hjermstad MJ, Viste A. Health-related quality of life in long-term survivors after high-dose chemoradiotherapy followed by surgery in esophageal cancer. Dis Esophagus 2011;24:39–47.
[10] Lin SH, Hobbs BP, Verma V, Tidwell RS, Smith GL, Lei X, et al. Randomized phase IIB trial of proton beam therapy versus intensity-modulated radiation therapy for locally advanced esophageal cancer. J Clin Oncol 2020;38:1569–79.
[11] Lin SH, Merrell KW, Shen J, Verma V, Correa AM, Wang L, et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer. Radiother Oncol 2017;123:376–81.
[12] Shiraishi Y, Xu C, Yang J, Komaki R, Lin SH. Dosimetric comparison to the heart and cardiac substructure in a large cohort of esophageal cancer patients treated with proton beam therapy or Intensity-modulated radiation therapy. Radiother Oncol 2017;125:48–54.
[13] 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.
[14] Xi M, Xu C, Liao Z, Chang JY, Gomez DR, Jeter M, et al. Comparative outcomes after definitive chemoradiotherapy using proton beam therapy versus intensity modulated radiation therapy for esophageal cancer: a retrospective, single-institutional analysis. Int J Radiat Oncol Biol Phys 2017;99:667–76.
[15] Engelsman M, Schwarz M, Dong L. Physics controversies in proton therapy. Semin Radiat Oncol 2013;23:88–96.
[16] Apolle R, Brückner S, Frosch S, Rehm M, Thiele J, Valentini C, et al. Utility of fiducial markers for target positioning in proton radiotherapy of oesophageal carcinoma. Radiother Oncol 2019;133:28–34.
[17] Hoffmann L, Poulsen PR, Ravkilde T, Bertholet J, Kruhlikava I, Helbo BL, et al. Setup strategies and uncertainties in esophageal radiotherapy based on detailed intra- and interfractional tumor motion mapping. Radiother Oncol 2019;136:161–8.
[18] Thomas M, De Roover R, van der Merwe S, Lambrecht M, Defraene G, Haustermans K. The use of tumour markers in oesophageal cancer to quantify setup errors and baseline shifts during treatment. Clin Transl Radiat Oncol 2020;5:8–14.
[19] Jin P, Hulshof MC, de Jong R, van Hooft JE, Bel A, Alderliesten T. Quantification of respiration-induced esophageal tumor motion using fiducial markers and four-dimensional computed tomography. Radiother Oncol 2016;118:492–7.
[20] 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.
[21] Møller DS, Poulsen PR, Hagner A, Dufour M, Nordsmark M, Nyeng TB, et al. Strategies for motion robust proton therapy with pencil beam scanning of esophageal cancer. Int J Radiat Oncol Biol Phys 2021.
[22] 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.
[23] Zhong H, Men K, Wang J, van Soest J, Rosenthal D, Dekker A, et al. The impact of clinical trial quality assurance on outcome in head and neck radiotherapy treatment. Front Oncol 2019;9.
[24] Brade AM, Wenz F, Koppe F, Lievens Y, San Antonio B, Iscoe NA, et al. Radiation therapy quality assurance (RTQA) of concurrent chemoradiation therapy for locally advanced non-small cell lung cancer in the PROCLAIM phase 3 trial. Int J Radiat Oncol Biol Phys 2018;101:927–34.
[25] Thomas M, Mortensen HR, Hoffmann L, Møller DS, Troost EGC, Muijs CT, et al. Proposal for the delineation of neoadjuvant target volumes in oesophageal cancer. Radiother Oncol 2021;156:102–12.
[26] Sloth Møller D, Knap MM, Nyeng TB, Khalil AA, Holt MI, Kandi M, et al. Difference in target definition using three different methods to include respiratory motion in radiotherapy of lung cancer. Acta Oncol 2017;56:1604–9.
[27] Underberg RWM, Lagerwaard FJ, Slotman BJ, Cuijpers JP, Senan S. Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer. Int J Radiat Oncol Biol Phys 2005;63:253–60.
[28] Thomas M, Defraene G, Lambrecht M, Deng W, Moons J, Nafteux P, et al. NTCP model for postoperative complications and one-year mortality after trimodality treatment in oesophageal cancer. Radiother Oncol 2019;141:33–40.

[29] Bosch DJ, Muijs CT, Mul VEM, Beukema JC, Hospers GAP, Burgerhof JGM, et al. Impact of neoadjuvant chemoradiotherapy on postoperative course after curative-intent transthoracic esophagectomy in esophageal cancer patients. Ann Surg Oncol 2014;21:605–11.
[30] Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G, et al. Benchmarking complications associated with esophagectomy. Ann Surg 2019;269:291–8.
[31] Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: A Secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. J Clin Oncol 2017;35:56–62.
[32] Banfill K, Giuliani M, Aznar M, Franks K, McWilliam A, Schmitt M, et al. Cardiac toxicity of thoracic radiotherapy: existing evidence and future directions. J Thorac Oncol 2021;16:216–27.
[33] Garant A, Spears G, Routman D, Whitaker T, Liao Z, Harmsen W, et al. A multi-institutional analysis of radiation dosimetric predictors of toxicity after trimodality therapy for esophageal cancer. Pract Radiat Oncol 2021;11:e415–25.
[34] Dess RT, Sun Y, Matuszak MM, Sun G, Soni PD, Bazzi L, et al. Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. J Clin Oncol 2017;35:1395–402.
[35] Wang K, Eblan MJ, Deal AM, Lipner M, Zagar TM, Wang Y, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy. J Clin Oncol 2017;35:1387–94.
[36] Nelms BE, Robinson G, Markham J, Velasco K, Boyd S, Narayan S, et al. Variation in external beam treatment plan quality: an inter-institutional study of planners and planning systems. Pract Radiat Oncol 2012;2:296–305.
[37] Das IJ, Cheng C-W, Chopra KL, Mitra RK, Srivastava SP, Glatstein E. Intensity-modulated radiation therapy dose prescription, recording, and delivery: patterns of variability among institutions and treatment planning systems. J Natl Cancer Inst 2008;100:300–7.
[38] Hoffmann L, Knap MM, Alber M, Møller DS. Optimal beam angle selection and knowledge-based planning significantly reduces radiotherapy dose to organs at risk for lung cancer patients. Acta Oncol 2021;60:293–9.
[39] Ge Y, Wu QJ. Knowledge-based planning for intensity-modulated radiation therapy: a review of data-driven approaches. Med Phys 2019;46:2760–75.
[40] Fogliata A, Belosi F, Clivio A, Navarria P, Nicolini G, Scorsetti M, et al. On the pre-clinical validation of a commercial model-based optimisation engine: application to volumetric modulated arc therapy for patients with lung or prostate cancer. Radiother Oncol 2014;113:385–91.
[41] Tol JP, Delaney AR, Dahele M, Slotman BJ, Verbakel WFAR. Evaluation of a knowledge based planning solution for head and neck cancer. Int J Radiat Oncol Biol Phys 2015;91:612–20.
[42] Berry SL, Ma R, Boczkowski A, Jackson A, Zhang P, Hunt M. Evaluating inter-campus plan consistency using a knowledge based planning model. Radiother Oncol 2016;120:349–55.
[43] Younge KC, Marsh RB, Owen D, et al. Improving quality and consistency in NRG Oncology Radiation Therapy Oncology Group 0631 for spine radiosurgery via knowledge-based planning. Int J Radiat Oncol Biol Phys 2018;100:1067–74.
[44] van den Ende RPJ, Peters FP, Harderwijk E, Rütten H, Bouwmans L, Berbee M, et al. Radiotherapy quality assurance for mesorectum treatment planning within the multi-center phase II STAR-TReC trial: Dutch results. Radiat Oncol 2020;15.
[45] Fenton PA, Hurkmans C, Gulyban A, van der Leer J, Matzinger O, Poortmans P, et al. Quality assurance of the EORTC 22043-30041 trial in post-operative radiotherapy in prostate cancer: results of the Dummy Run procedure. Radiother Oncol 2013;107:346–51.
[46] Lambrecht M, Clementel E, Sonke JJ, Nestle U, Adebahr S, Guckenberger M, et al. Radiotherapy quality assurance of SBRT for patients with centrally located lung tumours within the multicentre phase II EORTC Lungtech trial: Benchmark case results. Radiother Oncol 2019;132:63–9.
[47] Groom N, Wilson E, Lyn E, Faivre-Finn C. Is pre-trial quality assurance necessary? Experiences of the CONVERT Phase III randomized trial for good performance status patients with limited-stage small-cell lung cancer. Br J Radiol 2014;87:20130653.
[48] Meijers A, Jakobi A, Stützer K, Guterres Marmitt G, Both S, Langendijk JA, et al. Log file-based dose reconstruction and accumulation for 4D adaptive pencil beam scanned proton therapy in a clinical treatment planning system: Implementation and proof-of-concept. Med Phys 2019;46:1140–9.
[49] Jin P, van der Horst A, de Jong R, van Hooft JE, Kamphuis M, van Wieringen N, et al. Marker-based quantification of interfractional tumor position variation and the use of markers for setup verification in radiation therapy for esophageal cancer. Radiother Oncol 2015;117:412–8.