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Original Article

Robustness assessment of clinical adaptive proton and photon radiotherapy for oesophageal cancer in the model-based approach

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ABSTRACT

Purpose: In the Netherlands, oesophageal cancer (EC) patients are selected for intensity modulated proton therapy (IMPT) using the expected normal tissue complication probability reduction (ΔNTCP) when treating with IMPT compared to volumetric modulated arc therapy (VMAT). In this study, we evaluate the robustness of the first EC patients treated with IMPT in our clinic in terms of target and organs-at-risk (OAR) dose with corresponding NTCP, as compared to VMAT.

Materials and Methods: For 20 consecutive EC patients, clinical IMPT and VMAT plans were created on the average planning 4DCT. Both plans were robustly evaluated on weekly repeated 4DCTs and if target coverage degraded, replanning was performed. Target coverage was evaluated for complete treatment trajectories with and without replanning. The planned and accumulated mean lung dose (MLD) and mean heart dose (MHD) were additionally evaluated and translated into NTCP.

Results: Replanning in the clinic was performed more often for IMPT (15x) than would have been needed for VMAT (8x) ($p = 0.11$). Both adaptive treatments would have resulted in adequate accumulated target dose coverage. Replanning in the first week of treatment had most clinical impact, as anatomical changes resulting in insufficient accumulated target coverage were already observed at this stage. No differences were found in MLD between the planned dose and the accumulated dose. Accumulated MHD differed from the planned dose ($p < 0.001$), but since these differences were similar for VMAT and IMPT (1.0 and 1.5 Gy, respectively), the ΔNTCP remained unchanged.

Conclusion: Following an adaptive clinical workflow, adequate target dose coverage and stable OAR doses with corresponding NTCPs was assured for both IMPT and VMAT.

In thoracic radiotherapy, the radiation dose administered to the healthy tissues is associated with risks of pulmonary, cardiac, as well as post-operative complications [1–4]. The mean lung dose (MLD) is often described in literature as the dosimetric predictor for risk of radiation pneumonitis and is associated with overall survival [1,2,4]. More recent studies emphasize the need to reduce heart dose as well, as heart dose parameters were associated with overall survival and cardiac complications, occurring within the first months to years after radiotherapy [5–8]. Several studies have shown a large dose reduction in all organs-at-risk (OAR) while comparing proton to photon plans [9–11]. Recently, Lin et al.[12] demonstrated a marked reduction of the Total Toxicity Burden (TTB) after proton therapy compared to photon therapy in a randomized controlled trial. The TTB encompasses the most relevant (radiation-induced) complications that EC patients may experience after treatment. Additionally, post-operative hospital stay was shorter when patients were treated with proton therapy [13]. From March 2020, Dutch health care providers allowed to select EC patients for proton therapy in the neo-adjuvant setting to reduce severe complications and prolonged hospitalisation and intensive care stay during the COVID pandemic, following the model-based approach [14,15].

Although proton therapy has been shown to reduce OAR dose with consequent reduction in radiation-induced complications, concerns exist regarding the robustness of delivering the prescribed dose to the target volume [16,17]. The target volume is subject to inter- and intrafractional motion, which can cause geometrical uncertainties, and potentially create dose inhomogeneities due to interplay effects [18]. Interfractional displacements (e.g. anatomical and position variations) seem to

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have the largest impact on the target dose in a fully fractionated proton EC treatment [19,20]. Soft tissue changes, such as target deformations and diaphragm displacements, occur quite often in these patients, demanding replanning [11,21].

In this study, we evaluate IMPT robustness of the first 20 EC patients treated at our proton therapy centre by modern standards, as compared to VMAT. The planned and accumulated dose distributions are compared in terms of target coverage and OAR dose with corresponding normal tissue complication probability (NTCP), according to the Dutch indication protocols used for model-based patient selection. Furthermore, the effects of replanning are considered by comparing adaptation schemes. In this way, we aim to validate the sustainability of target coverage and patient selection over the complete radiotherapy treatment course.

Methods and materials

Model-based patient selection

Between March 2020 and June 2021, EC patients who were eligible for neo-adjuvant chemoradiotherapy (nCRT) and surgery, were selected for IMPT in our clinic based on a temporary indication protocol (TIP), in accordance with the model-based selection approach [14,15]. In this approach, multivariable prediction models for the risk of complications are being used to translate OAR dose into NTCP. The TIP included a multivariable prediction model for the risk of a TTB $\geq$60 ($NTCP_{TIP}$), which was developed in an independent cohort of EC patients [22,23]. The $NTCP_{TIP}$-model (including age and MLD as predictors) can be used to calculate the $NTCP_{TIP}$ for both a VMAT and an IMPT plan by:

$$NTCP_{TIP} = \frac{1}{1+e^{-A}},$$

$$\text{where A} = -4.083 + (0.039 * age[years] + (0.092 * MLD[Gy])$$

As of July 2021, EC patients treated with nCRT are being selected for IMPT based on a new indication protocol (NIP), which is based on an externally validated multivariable prediction model for 2-years mortality after treatment including mean heart dose (MHD) and the volume of the gross target volume (GTV) as predictors [24,25]. The 2-years mortality risk estimate is considered a surrogate for the (cardiac) complication risk and is calculated by:

$$NTCP_{NIP} = \frac{1}{1+e^{-B}},$$

$$\text{where B} = -3.0352 + 0.100 * \sqrt{(GTV[cm^3])} + 0.4457 * \sqrt{(MHD[Gy])}$$

According to both TIP and NIP, the difference in NTCP between VMAT and IMPT (ΔNTCP) must be larger than 5 % to qualify for IMPT. Both strategies of the model-based approach are shown in Fig. 1. For all patients, the NTCP estimations were calculated nominally (at baseline) and after dose accumulation, to evaluate its robustness throughout treatment.

Other than not complying to the selection criteria of the TIP, patients did not receive IMPT when metal parts were in the beam path or large target/diaphragm motion was observed in the planning 4DCT. The motion was assessed by evaluating the extreme phases of the planning 4DCT. A deformable image registration (DIR) was created between the end-of-expiration and end-of-inspiration phases using the ANACONDA DIR available in RayStation, and the subsequent motion vectors were analysed [26]. Patients with target motion below 15 mm and diaphragm motion below 22 mm were considered suitable for IMPT. For target or diaphragm motion exceeding these thresholds, the decision to treat with IMPT or VMAT was further assessed by a radiation oncologist and a physicist, considering the magnitude of motion and its location.

Patient data

Our standardised follow-up program was approved by the medical ethics committee (METc2014.379). All surviving patients provided informed consent. The patients were treated with robustly optimised IMPT, after plan comparison with VMAT as part of the model-based approach. Both plans were made on the average 4DCT at baseline, following the internal target volume (ITV) concept. Delineation and treatment planning details can be found in the Supplementary Materials (Supp. A).

Dose verification during treatment

During treatment, weekly repeat 4DCTs were acquired and the ITV was redelineated on the average CT. The IMPT plan was evaluated both nominally, and robustly including 2 mm setup errors and 3 % range uncertainty [11,20,27,28]. The 2 mm setup error accounts for residual errors after patient alignment, such as intrafractional patient variation, isocentre and positioning accuracy. Consistently, nominal and robustness evaluation was performed for the VMAT plans as well (including only setup errors). If the dose that 98 % of the ITV receives ($D_{98\%}$) was < 96 % on the voxel-wise minimum dose distribution (Vw_{min}), the treating physician decided if replanning was necessary by visual inspection of the dose distribution [28]. For VMAT this was performed retrospectively. For all cases with $D_{98\%} \geq$96 %, target coverage was assumed to be adequate. Both the initial plan and all adapted plans were evaluated over all treatment weeks.

Evaluation of dose accumulation

Treatment trajectories were created for all patients and both techniques with and without (multiple) replanning. The majority of the patients underwent five repeated CTs. To accumulate the dose for the full treatment of 23 fractions, five fractions were assigned each to the first four weekly CTs and three to the last weekly CT. For the trajectories including replanning, the replan started on the same fraction as in the clinic. As this information was not available for the VMAT plans, we considered the same replanning time as for IMPT.

The weekly nominal and Vw_{min} dose distributions were accumulated on the planning CT to evaluate the OAR dose and the target dose coverage, respectively, simulating the actual given dose for various trajectories. Before accumulation, dose warping was performed using the ANACONDA DIR from the repeated average CT to the planning average CT. The ITV was used as a controlling region-of-interest (ROI) to optimise the DIR and the subsequent dose warping [29]. A $D_{98\%} \geq$96 % of the ITV on the Vw_{min} was considered acceptable accumulated ITV dose coverage. For all other cases, three radiation oncologists were asked to rate the target dose coverage as being unacceptable, borderline (just good enough) or acceptable. The MLD and MHD were evaluated after nominal dose accumulation and the corresponding NTCP according to the TIP and NIP. The non-parametric Wilcoxon signed-rank test was used to show statistical differences between IMPT and VMAT.

Results

The evaluated patient population consisted of the first 20 patients treated in our clinic with IMPT between April and November 2020, following the TIP for EC (Table 1). Five patients were excluded from IMPT, due to a ΔNTCP < 5 % (n = 1) or due to large target/diaphragm motion (n = 4). The median $\Delta NTCP_{TIP}$ was 9.4 %,

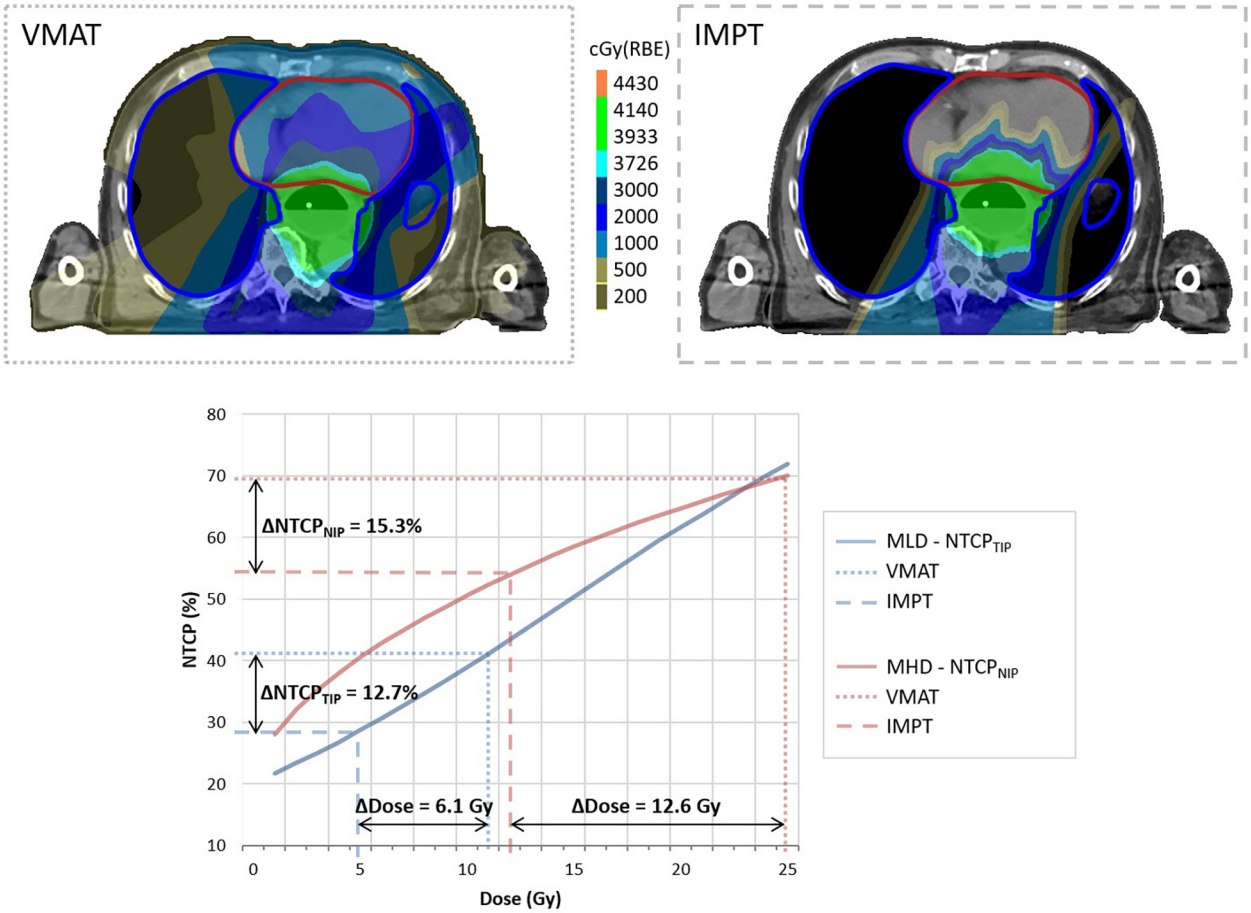

Fig. 1. For patient selection in the model-based approach, a plan comparison is performed between a photon (VMAT) and a proton (IMPT) plan. The dose difference in MLD and MHD translates into a ΔNTCP, according to the TIP and NIP, respectively. In this patient (patient 7), a MLD difference of 6.1 Gy was found, which corresponded to a complication reduction of 12.7 %. The MHD reduction was 12.6 Gy, which corresponded to a ΔNTCP of 15.3 %.

Table 1
Patient characteristics.

		n = 20
Age	mean (range)	62.6 (48–75)
GTVp size (cm^3)	mean (range)	68.7 (8–273)
Target motion (mm)	mean (range)	11.5 (5–17)
Diaphragm motion (mm)	mean (range)	14.7 (8–22)
Staging	T2N0	4
	T2N1	3
	T2N2	1
	T2-3 N0	1
	T3N0	4
	T3N1	5
	T3N2	2
Histology	Adenocarcinoma	17
	Squamous cell carcinoma	3
Location	Proximal-Middle-Distal	2
	Proximal-Middle	1
	Middle	2
	Middle-Distal	15

and the median $\Delta NTCP_{NIP}$ 11.4 %. Both the TIP and NIP data is summarised for all patients in Fig. 2.

Naturally, the NTCP reductions observed in the IMPT group resulted from the lower MLD and MHD found in IMPT compared to VMAT. We found the median MLD to be 8.4 Gy and 3.2 Gy for VMAT and IMPT, respectively ($p < 0.001$) (Fig. 2). Besides the mean dose, we found reductions in the median lung volume receiving 20 Gy (V20: 9.9 % vs 7.3 %, [$p < 0.001$]) and receiving 5 Gy (V5: 55.2 % vs 13.6 %, [$p < 0.001$]) for IMPT. The median MHD decreased from 15.3 Gy in the VMAT plans to 8.1 Gy for the IMPT plans ($p < 0.001$) (Fig. 2). Patient 8 showed the largest MHD difference between VMAT and IMPT (ΔMHD) of 13.5 Gy. We found similar median heart volumes receiving 30 Gy (11.4 % vs 11.2 % for IMPT and VMAT, $p = 0.794$). Additionally, the median mean spleen dose (9.5 Gy vs 3.4 Gy, $p < 0.001$) and mean liver dose (9.0 Gy vs 2.1 Gy, $p < 0.001$) was lower with IMPT compared to VMAT.

Considering the adaptive VMAT and IMPT trajectories, the initial MLD difference between the VMAT and the IMPT plan (ΔMLD) was only slightly different than the accumulated ΔMLD (mean difference 0.2 Gy, $p = 0.970$). For the MHD, the mean difference between the planned dose and the accumulated dose was 1.3 Gy ($p < 0.001$) and for 11 cases a difference of more than 2 Gy was observed. Here, the MHD was slightly more consistent in the VMAT plans (1.0 Gy mean difference) compared to the IMPT plans (1.5 Gy mean difference). However, large differences were observed for both techniques and not always consistent between techniques. For three patients with differences > 3 Gy, the MHD was additionally evaluated on each weekly CT (Supp. B [Supplementary Materials]), which showed changes in MHD over the treatment course. The largest increase of MHD in IMPT comparing the accumulated to the planned dose (from 6.6 Gy to 9.8 Gy for patient 17), resulted in a decreased $\Delta NTCP_{NIP}$ from 13.9 % to 11.3 %. However, over all patients, both the median planning $\Delta NTCP_{NIP}$ and the accumulated $\Delta NTCP_{NIP}$ was 10.8 %. The small MLD changes between the planned and accumulated dose had no impact on the $NTCP_{TIP}$. Fig. 2 sum-

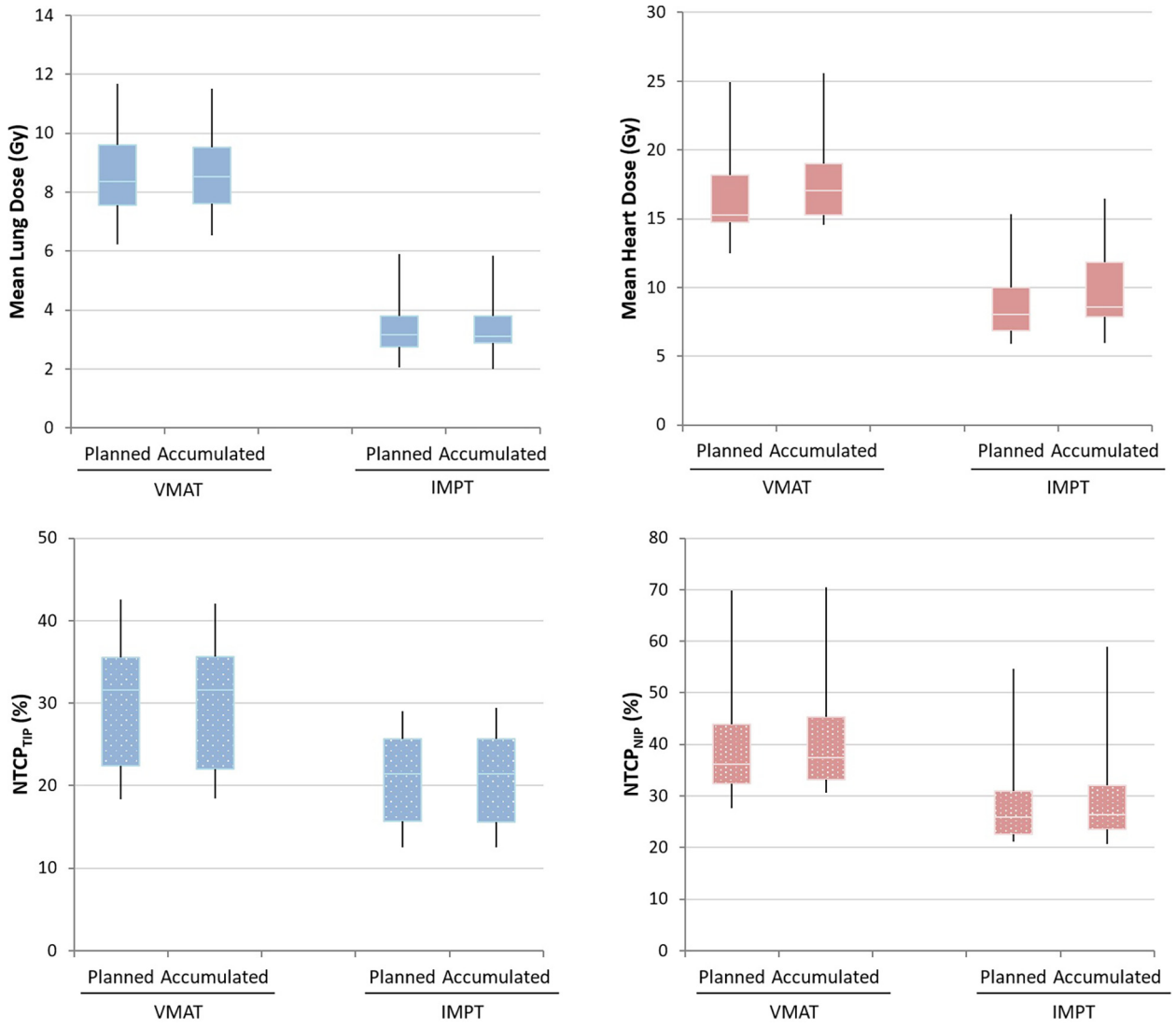

Fig. 2. For both VMAT and IMPT, the mean lung dose and the mean heart dose were evaluated at planning stage and after dose accumulation of the adaptive treatment trajectories. The corresponding NTCP was analysed additionally. The whiskers represent the range of values, the boxes represent the quartiles and the horizontal line is the median value.

marises planning and accumulated MLD and MHD with corresponding NTCP. For all patients and for both TIP and NIP, the ΔNTCP was above the 5 % threshold in the accumulated dose.

Dose differences between the replanning trajectories regarding OAR were only observed for MHD. The largest difference was seen in IMPT for patient 12; the accumulated MHD was 4.4 Gy lower after replanning, compared to no replanning. This effect was caused by a caudal diaphragm displacement that had in this patient less impact on VMAT (0.9 Gy difference). Generally, replanning restored the accumulated MHD to the planning situation.

Replanning was generally indicated for ITV coverage $D_{98\%}$ <94 % on the Vw_{min}. Visual inspection of the target dose coverage was performed, which also resulted in replanning for some cases in which ITV dose coverage ($D_{98\%}$) was 94 %-95 %. The replanned IMPT plan was clinically available after five working days on average, ranging from three to seven days.

Replanning was indicated 8 times for VMAT and 15 times for IMPT in total (p=0.11). For patient 4, replanning was unavoidable, as the patient could not go through with treatment with the arms up. For the remaining 19 patients, all replanning information and target dose coverage evaluation of the different treatment trajectories is shown in Fig. 3. We analysed all causes of inadequate target dose coverage that indicated replanning (Fig. 4). The only reason for VMAT replanning was a diaphragm displacement. In three out of the seven VMAT replanning indications, replanning was not required for IMPT. For IMPT, diaphragm displacements and/or target deformations were the most frequent cause of inadequate dose coverage. Other reasons for IMPT replanning were changes in patient positioning, oesophagus dilatation, changes in lung density and intra-observer delineation variability.

The adaptive treatment trajectory resulted in borderline or acceptable accumulated target dose coverage for all patients and both techniques (Fig. 3). Borderline dose coverage ranged from $D_{98\%}$ 90–95 % and acceptable coverage from $D_{98\%}$ 94 %. Some underdosage in the elective abdominal area did not result in unacceptable coverage as rated by the clinicians. Without any replanning, unacceptable accumulated target coverage was found for three patients in VMAT and five patients in IMPT. No unacceptable accumulated target coverage remained when the first replanning (if indicated) was taken into account. A second replan was performed five times, but only changed the outcome for patient 17, from borderline to acceptable. For patient 12, suffering from weekly

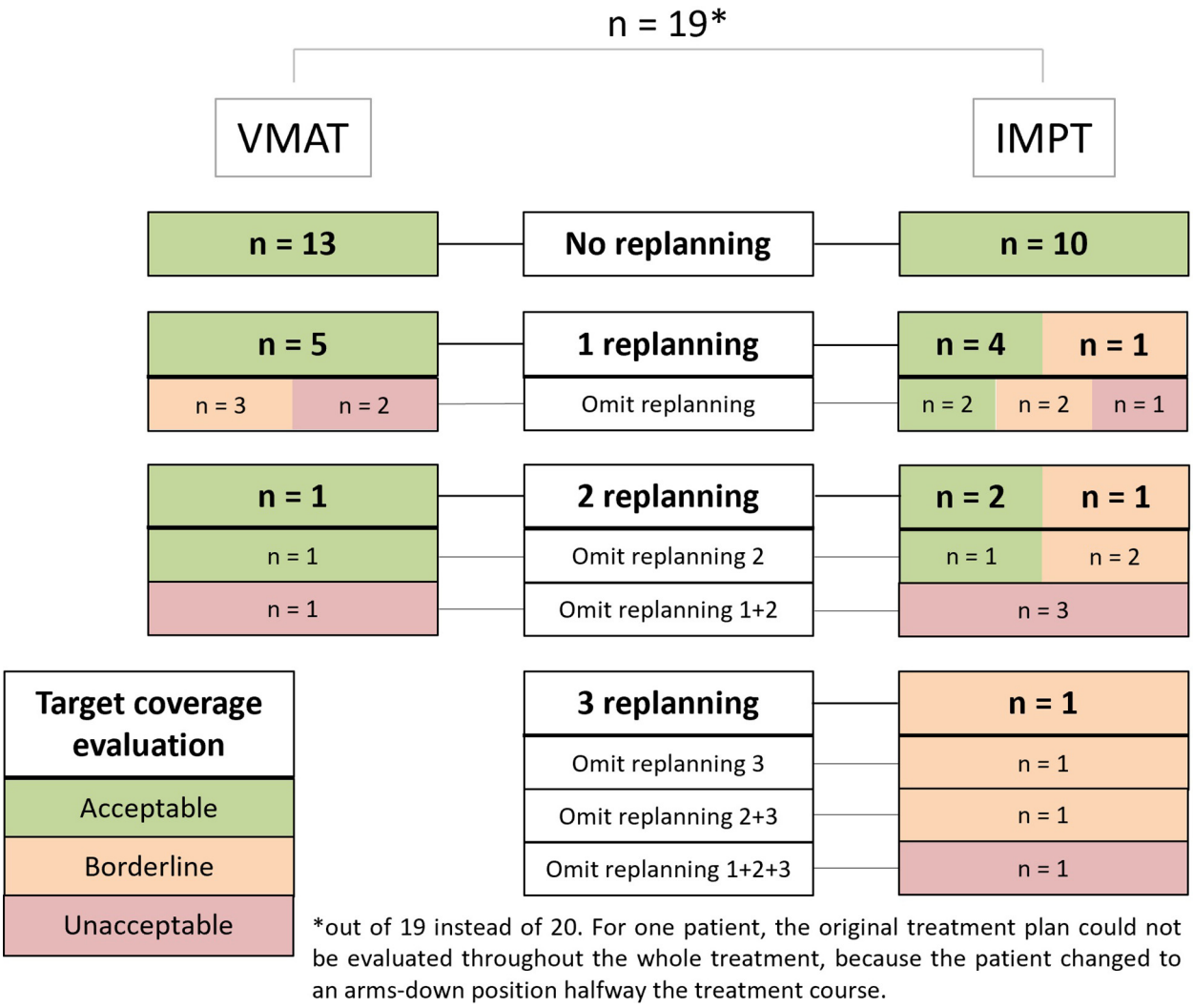

Fig. 3. Illustration of performed replanning for all patients for the VMAT and IMPT plans based on the weekly target coverage evaluation (upper boxes) and target coverage evaluation of the corresponding accumulated treatment trajectories. For every replanning case, the trajectory without replanning is additionally evaluated (lower boxes).

changes in diaphragm position resulting in multiple replanning, accumulated target dose coverage was still borderline for adapted IMPT ($D_{98\%}$ = 92 %). VMAT required only one replan for this patient, which resulted in an acceptable $D_{98\%}$ of 97 %. For another patient (#11), the target coverage of the IMPT plan was so low in the first week, that it could only be restored to a borderline accumulated target coverage ($D_{98\%}$ 93 %) although all other weeks had adequate dose coverage with the replan. For VMAT, acceptable accumulated target dose coverage was observed including one replan ($D_{98\%}$ 98 %). Replanning later than the first treatment week occurred once for VMAT and eight times for IMPT, but the accumulated target coverage only improved for two of these replans, from borderline to acceptable. The initiation of the replan in the treatment trajectory is included in Fig. 5.

Discussion

In this study, we investigated the robustness of our clinical VMAT and IMPT plans in the neo-adjuvant treatment of EC [30,31]. Without replanning, target dose coverage was insufficient in 3/20 and 5/20 patients for VMAT and IMPT, respectively. Therefore, frequent monitoring and dose evaluation is required for safe treatment with IMPT, but also for VMAT.

Most of the causes that indicated replanning were persistent and led to a systematic underdosage of the target volume if not replanned. Target deformations resulted in range errors and geometrical displacements, which affected the IMPT plans more than the VMAT plans in terms of target robustness. This might be related to the limited beam angles and increased sensitivity to density changes for IMPT. Anakotta et al.[11] also described pleural effusion and gastric filling as reasons for IMPT replanning. The latter can be avoided by using posterior beams as done in this study [11,19,32]. The current study showed that the displacement of the diaphragm is the most frequent reason for inadequate dose coverage indicating replanning. These displacements affected the VMAT plans more than the IMPT plans, due to the lateral dose contribution through the diaphragm region in VMAT. Moreover, as a consequence of increased awareness for cardiac dose reduction, the lateral beam contribution of the VMAT plans increases even further. This dose disturbance in photon plans was also confirmed by Møller et al.[21], who showed single uniform dose proton plans to be more robust to these anatomical changes than intensity-modulated radiotherapy photon plans after evaluation on a CT in the second week of treatment. Our results indicate that these displacements often already occur in the first treatment week and persist for most patients. To handle diaphragm displacements, online adaptation for photon therapy, as nowadays possible with

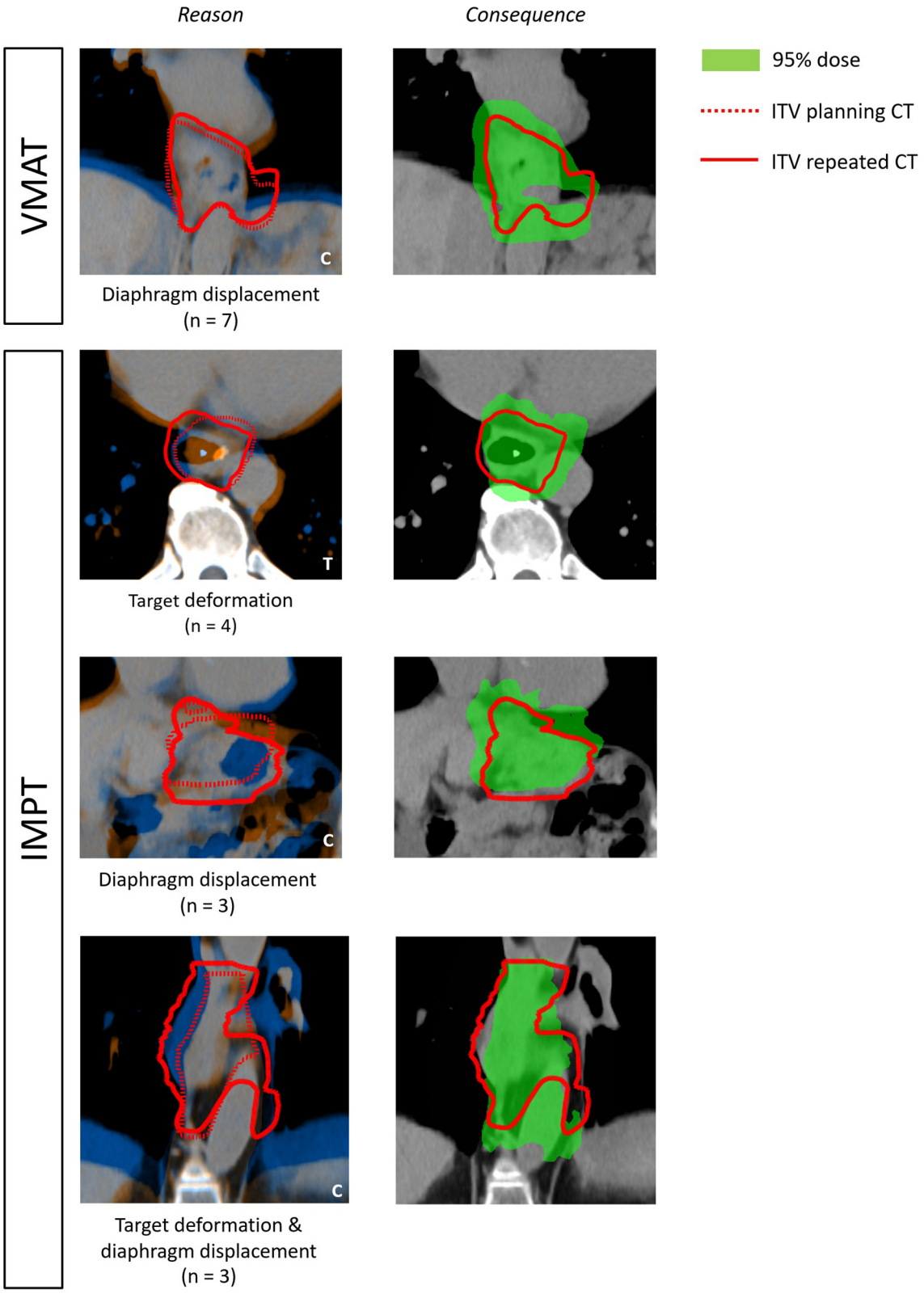

Fig. 4. The most frequent reasons for replanning of VMAT and IMPT visualised in the coronal (C) or transversal (T) view. VMAT and IMPT were replanned respectively seven and fourteen times in total due to inadequate dose coverage. On the left, the registration of the average CT of week 1 (in blue) to the average planning CT (in orange) is shown, to visualise the reason for replanning (including its frequency). On the right, the consequence of this is shown in terms of target dose coverage on the voxel-wise minimum dose distribution.

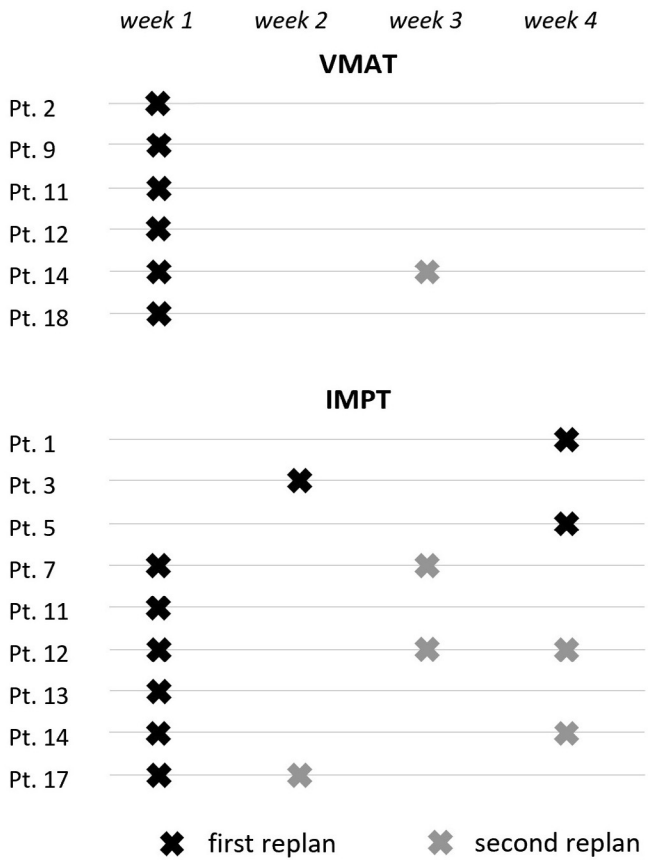

Fig. 5. Timeline of indicated replanning in the adaptive treatment trajectories when target coverage was found insufficient based on the weekly evaluation. The replan was on average initiated five working days (one week) later.

MRI or CT, could be a potential solution [33,34]. In our clinic, we have deployed a diaphragm-based position verification workflow for observed diaphragm displacements above 8 mm on daily pre-treatment CBCTs to improve daily target dose coverage [35]. These corrections for the diaphragm position were not taken into account in the current work, but would potentially improve the target evaluation outcomes further.

The accumulated dose trajectories provided insight in the effects and necessity of replanning. All VMAT replanning performed was actually required to obtain acceptable accumulated target dose, whereas for IMPT, some replanning would not have been necessary retrospectively. Especially replanning after the first treatment week generally did not result in a change of outcome. These results indicate that the CT in the first treatment week is the most important to detect anatomical variations and the need for replanning. Furthermore, it is crucial to initiate the replan as soon as possible to limit the effect of the anatomical change and subsequent dose deviations. For one patient (#11), the replan was effectuated too late for the accumulated target dose coverage to be acceptable. When the severe underdosage was observed for this patient in the clinic, new VMAT and IMPT plans were made on the most recent CT. Since the VMAT plan was available sooner, this patient was transferred to the photon clinic for a few fractions, while waiting on the new IMPT plan.

Replanning also helped to restore initial planning OAR dose, especially for the MHD. No differences were found comparing the MLD of the planned and accumulated dose, resulting in consistent $\Delta NTCP_{TIP}$. Dose differences in MHD, comparing accumulated dose to the planning dose, were larger for smaller volumed hearts, and could be linked to diaphragm displacements. As the difference of MHD was quite consistent for both VMAT and IMPT along the treatment course, this resulted in a more or less consistent $\Delta NTCP_{NIP}$. Moreover, differences were relatively small compared to the large NTCP reductions by IMPT and did not change the patient selection.

Target coverage robustness was evaluated weekly based on the weekly CT, and the full course dose was evaluated by accumulation over all CTs. As a result of the available imaging for dose calculations, only one anatomy per week is considered, which is a limitation of this study. The addition of CTs could deteriorate the target coverage results if the anatomies deviate more. However, the effect of dose smoothening is likely to improve the results. In the future, we aim to reconstruct daily doses with the use of synthetic CTs from CBCTs [36]. For all patients included in this study, a visual check between daily CBCTs and the weekly CT has been performed by medical physicists to investigate the representativity of the CT for the whole week.

The estimated NTCP in this study results from the model-based approach applied in our clinic, following the respective indication protocols. The calculated ΔNTCP provides an indication of the potential benefit that can be expected of IMPT compared to VMAT in terms of complication risk reductions, and is used for patient selection. Soon we hope to verify that these dose reductions actually translate in lower complications for our patients. Patients were selected with the TIP (based on MLD), and are currently selected with the NIP (based on MHD). However, using only these parameters, the benefit of proton therapy might be underestimated. In this study, we have shown that the largest reductions exist in the low dose areas for lungs and heart. Additionally, dose to the spleen and liver were much lower for IMPT. In line with this, Shiraishi et al.[37] showed significant risk reduction of lymphopenia grade 4 for patients treated with proton therapy compared to intensity modulated radiotherapy, which was associated with worse overall survival and less pathological complete responders [38,39]. Not only dose to the spleen, but also the dose to the heart and large vessels might be relevant to limit this risk. With proton therapy, the dose to all these regions is lower compared to state-of-the-art photon therapy. In the future, the aim is to further improve the selection of patients based on all relevant complication reductions to be able to encompass the entire benefit of proton therapy.

Conclusion

Our clinical offline adaptive workflows for VMAT and IMPT ensured adequate target dose coverage in all patients. Replanning was necessary for both techniques, as regions in the thorax are subject to anatomical variations. Generally, one replanning was sufficient for adequate dose coverage in both VMAT and IMPT. Frequent monitoring of the patient anatomy and its influence on the dose distributions is required, especially in the first treatment week. Additionally, the adaptive workflow showed that ΔNTCP based on MLD and MHD were consistent over treatment, assuring that model-based patient selection using baseline plans is justified.

Conflict of interest notification

Dr. Langendijk reports personal fees from IBA, other from IBA, other from Philips, other from MIRADA, other from RaySearch, other from Siemens, other from Elekta, other from Leonie, outside the submitted work. As of 01/09/2021C. Oraboni Ribeiro is full-time employee of Ion Beam Applications S.A. (IBA). This study has been performed prior to that. No financial or in-kind contributions from IBA have been received.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.11.001.

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