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Original Article

An online adaptive plan library approach for intensity modulated proton therapy for head and neck cancer

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ABSTRACT

Background and purpose: In intensity modulated proton therapy (IMPT), the impact of setup errors and anatomical changes is commonly mitigated by robust optimization with population-based setup robustness (SR) settings and offline replanning. In this study we propose and evaluate an alternative approach based on daily plan selection from patient-specific pre-treatment established plan libraries (PLs). Clinical implementation of the PL strategy would be rather straightforward compared to daily online re-planning.
Materials and methods: For 15 head-and-neck cancer patients, the planning CT was used to generate a PL with 5 plans, robustly optimized for increasing SR: 0, 1, 2, 3, 5 mm, and 3% range robustness. Repeat CTs (rCTs) and realistic setup and range uncertainty distributions were used for simulation of treatment courses for the PL approach, treatments with fixed SR (fSR_3) and a trigger-based offline adaptive schedule for 3 mm SR (fSR_3OfA). Daily plan selection in the PL approach was based only on recomputed dose to the CTV on the rCT.
Results: Compared to using fSR_3 and fSR_3OfA, the risk of xerostomia grade $\geq$ II & III and dysphagia $\geq$ grade III were significantly reduced with the PL. For 6/15 patients the risk of xerostomia and/or dysphagia $\geq$ grade II could be reduced by > 2% by using PL. For the other patients, adherence to target coverage constraints was often improved. fSR_3OfA resulted in significantly improved coverage compared to PL for selected patients.
Conclusion: The proposed PL approach resulted in overall reduced NTCPs compared to fSR_3 and fSR_3OfA at limited cost in target coverage.

The accuracy of Intensity Modulated Proton Therapy (IMPT) delivery may be compromised by setup errors, range errors and anatomical changes [1–5]. The clinical challenge is to maintain adequate target coverage during the fractionated treatment, while maximally sparing organs-at-risk (OARs).

In current clinical practice, the sensitivity to setup errors, range errors and anatomical changes is often mitigated by a combination of scenario-based mini-max robust treatment planning with isotropic setup (SR) and range robustness (RR) settings [6,7], and offline adaptive replanning in case the original robust plan is no longer adequate for the changed anatomy [8]. The SR setting is generally fixed for the patient population and the treatment course, using a value that ensures target coverage for the vast majority of patients [9]. This may lead to an overly conservative SR setting for patients with relatively small geometrical variations during the treatment course [10,11]. Especially for head and neck (H&N) cancer patients, with critical organs typically close to the target, this results in a potentially avoidable enhanced risk of long term side effects [10,12,13]. On the other hand, for patients with relatively large geometrical variations, the fixed SR setting may also result in reduced target coverage [14–16]. Dose degradation due to slowly developing changes in patient geometry, e.g. related to weight loss, may be mitigated with offline adaptive replanning. However, this process is lengthy and labor intensive, and cannot account for daily inter-fraction geometrical variations.

Theoretically, adverse dosimetric effects of gradual and inter-fraction variations can be avoided by online treatment plan re-optimization. The generated adapted daily plan would solely need to be robust against range errors, machine related setup uncertainties and intra-fraction geometrical variations. Despite various promising efforts to develop online optimization strategies for IMPT [17–20], clinical introduction remains challenging. This is mainly due to limitations in algorithms for automated contouring

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of targets and OARs, fast and safe procedures for plan quality assurance (QA), calculation times and additional workload [21].

To mitigate and reduce some of the challenges of daily adaptive re-optimization, online adaptive use of a patient-specific plan library (PL) could possibly be used as an alternative. In this approach, prior to the start of a fractionated patient treatment, a set of plans is generated for a range of different patient anatomies or margins, referred to as a plan library. The patient is treated with the library plan that best fits the geometry-of-the-day as determined using daily imaging. In photon therapy, PL strategies have already been clinically implemented for mitigation of dose degradations related to inter-fraction anatomical variations in rectal, bladder and cervical cancer patients [22–29]. For cervical cancer proton therapy, Jagt et al. (2019) [30] introduced a PL that is used to warm start an online reoptimization of the daily treatment plan, and Van der Schoot et al. (2016) [31] compared the potential dosimetric advantages of PL-based IMPT treatments to PL-based VMAT treatments.

In this study, an online adaptive PL strategy for H&N cancer IMPT was developed and evaluated. PLs were composed of a set of plans generated using the initial planning CT-scan and robust optimization with different SR settings for each plan. For each fraction, the plan with the smallest SR that met the clinical target volume (CTV) coverage criteria on a daily in-room CT was selected. In this way, the PL approach should allow treatment fractions with appropriate setup robustness setting for daily anatomical variations. This PL workflow would be less demanding in a clinical setting compared to daily online reoptimization.

The aim of this study was to evaluate the possibility to decrease normal tissue complication probabilities (NTCPs) and increase CTV coverage with a practical PL strategy compared to treatments with a fixed robust treatment plan and an offline adaptive treatment strategy.

Materials and methods

Patient data

Fifteen H&N cancer patients treated with IMPT as primary treatment at Holland Proton Therapy Center (HollandPTC) in 2019 and 2020 were included. Inclusion criteria were 1) availability of at least 3 repeat CTs (rCTs), acquired in treatment position during the fractionated treatment to verify the need for offline replanning due to anatomical changes and 2) no sacrifice of robust target coverage in the clinical treatment plan due to OARs constraints in close proximity to the target. The rCTs were scheduled as part of the standard protocol, and the frequency per patient was based on the availability of personnel and CT scanner. Patients were selected for IMPT through a model-based selection protocol [32] and were treated with 70 Gy_{RBE} to the gross disease sites (CTV_{7000}) and 54.25 Gy_{RBE} to the elective areas (CTV_{5425}) using a constant relative biological effectiveness (RBE) of 1.1. During clinical treatment, 9 plan adaptations were performed for 7 patients in total. Four plan adaptations were performed on the last CT. Clinical decisions to replan were based on a combination of evaluation of sequential daily CBCTs and recomputation of the dose on the rCT. Patient characteristics and treatment information are shown in Table 1.

Al CTs were acquired with an out-of-room CT scanner (SOMATOM Definition Edge, Siemens Healthineers, Erlangen, Germany) in treatment position. Due to artifacts, some areas of the CTs required a density override with either muscle, air or water. For the purpose of this study, we assumed that these CTs were acquired with the in-room CT on rails system (SOMATOM Confidence CT, Siemens Healthineers, Erlangen) that has been integrated with our proton therapy system (ProBeam 4.0, Varian Medical Systems, Palo Alto, United States). Recently, this system has been commissioned for adaptive proton therapy, i.e. the CT scan with the patient on the treatment couch can be used directly to evaluate and adapt the treatment plan. Patients were immobilized using a BoS™ Headframe Mask and a MOLDCARE® Head Cushion (Qfix, Avondale, United States) and positioned using a laser system. Before each treatment fraction, a CBCT was acquired at the gantry and matched to the planning CT (pCT), followed by a 6-D couch correction (translational shifts, pitch, roll and yaw).

Target contours were propagated from pCTs to corresponding rCTs. CTV_{7000} and the part of the CTV_{5425} that was a 5 mm margin to the CTV_{7000} were rigidly propagated from the pCT to the rCTs and were manually adjusted (by M.O.) if contours were outside the external patient contour or inside bone. The remainder of the CTV_{5425} was deformably propagated to the rCTs and manually adjusted to visually match the contour on the pCT in case of visible deviations from the pCT contour. For Patient 1, the location of the CTV_{7000} was adjusted at rCT 3 and 4 because of anatomical changes that impacted the target location. The contours were checked for consistency by expert clinicians (M.K. and S.Hu.).

Generation of treatment plans

For each patient, five different plans with varying SR settings (0, 1, 2, 3 or 5 mm) were optimized fully automatically on the pCT using our in-house TPS, Erasmus-iCycle [34–37]. The RR was set to 3% for all plans.

Erasmus-iCycle was configured to generate treatment plans that were similar to the clinical treatment plans. Erasmus-iCycle uses the Astroid dose engine [38], which was configured for our clinical beam characteristics (ProBeam 4.0, Varian Medical Systems, Palo Alto, United States), having spot sizes between 3.3 mm at 244 MeV and 5.9 mm at 70 MeV (1 standard deviation) in air at isocenter without range shifter. More details regarding robust treatment plan generation with Erasmus-iCycle can be found in Appendix A in the supplementary material.

For the patients who received an offline plan adaptation in the clinical treatment schedule, a new treatment plan was created for the relevant rCT for evaluation of the offline adaptive strategy. These plans were not included in the PL.

Daily plan selection

In the PL strategy, daily plan selection from the PL was automatically performed in a step-wise approach based on the recomputed dose distributions of all PL plans on the rCT in the nominal scenario. In the first step, all library plans with $D_{2\%}$ in CTV_{7000} > 110% of the prescribed dose for a fraction were excluded. Next, the plan with the smallest SR setting that adhered to CTV $V_{95.5\%}$ > 98% was selected. The envisioned PL clinical workflow is depicted for an example patient in Appendix B in the supplementary material. Fractions were equally spread over the available rCTs.

In the treatment schemes using a fixed robust treatment plan (fSR), the same plan was used for every fraction. Treatments with a 0, 1, 2, 3 and 5 mm SR setting for every fraction were evaluated. Offline plan adaptations were not considered. These treatments will be referred to as fSR_{SR}.

The offline adaptive scheme was evaluated for 3 mm SR plans, and will be referred to as fSR_3OfA. Plan adaptations were performed on rCTs based on the clinical decision to perform an adaptation (Table 1). The adapted plan was simulated to be used from the next rCT onwards. Adaptations on the last rCT were therefore not taken into account in the evaluation since they could only be applied on the next rCT. This resulted in a total of 5 plan adaptations for 5 patients (1, 7, 10, 12 and 15) that were performed.

Table 1
Patient characteristics and treatment information. Abbreviations: Clinical Target Volume (CTV), planning CT (pCT), repeat CT (rCT), Tumor (T), Node (N) stage in correspondence to [33], Common Terminology Criteria for Adverse Events (CTCAE).

	Tumor site	Volume CTV_{7000} (cm^3) pCT	Volume CTV_{5425} (cm^3) pCT	Number of rCTs	Plan adaptation at rCT during clinical treatment	T	N	Baseline Xerostomia (0–3 CTCAE)	Baseline Dysphagia (0–5 CTCAE)
Patient 1	Tongue base	97.3	431.5	4	3,4*	1b	2	0	1
Patient 2	Hypopharynx	49.7	346.9	6		2	1	1	1
Patient 3	Oropharynx	147.4	493.7	5		4a	1	0	1
Patient 4	Oropharynx	115.2	428.3	3		4a	2c	0	1
Patient 5	Nasopharynx	221.3	524.6	5		1a	2a	0	0
Patient 6	Oropharynx	37.3	212.2	5		4a	0	0	0
Patient 7	Oropharynx	136.4	473.6	4	3	1a	1	0	0
Patient 8	Tonsil	44.1	252.2	3		2	0	0	1
Patient 9	Tonsil	96.0	313.7	4	4*	1b	1	1	0
Patient 10	Nasopharynx	227.8	527.9	5	4	1a	2	0	0
Patient 11	Hypopharynx	114.2	304.5	4	4*	2	2b	0	1
Patient 12	Nasopharynx	190.9	437.6	4	2	2**	2**	0	0
Patient 13	Oropharynx	117.9	342.2	6		2	1	0	1
Patient 14	Nasopharynx	210.4	520.1	6		2	2	0	0
Patient 15	Tongue base	142.2	364.9	4	1,4*	2	1	0	0

* Plan adaptation not taken into account in offline adaptive schedule, because it was performed on the last rCT.
** TNM-7 data because TNM-8 was not available.

The remaining 10 patients were also included in the analysis of fSR_3OfA and were simulated without adaptation. Note that for these patients, the obtained values in fSR_3OfA are therefore equal to fSR_3.

Evaluation - Simulation of treatments

For all evaluated treatment strategies ($fSR_{0\text{-}5}$, fSR_3OfA and PL), 25 treatment courses of 35 fractions were simulated using a similar approach as Kraan et al. (2013) [39] and Wagenaar et al. (2021) [10]. For each simulated treatment course, one systematic setup error, one systematic range error and 35 random setup errors were randomly generated from Gaussian distributions and applied to the rCTs by isocentric and density shifts after first performing a rigid 6-D match between the rCT and pCT. The same errors were applied to the different treatment strategies. The standard deviations (SD) of the Gaussian distributions were derived from QA data at HollandPTC, and included the squared sum of the isocentric errors in the CT (systematic) and gantry (systematic and random), uncertainties in couch positioning (random), registration with the MR (systematic), online matching (random) and intra-fraction motion (systematic and random). This resulted in SDs of 0.88, 0.88 and 0.91 mm for the systematic setup errors, and 0.78, 0.75 and 0.82 mm for the random errors in lateral, longitudinal and vertical directions, respectively [11]. Inter and intra observer variations in contouring were not considered. The Gaussian distribution of range errors was assumed to have a SD of 1.5% in correspondence to [40].

Evaluation - Dosimetric evaluations and comparisons

The PL treatments were compared to fSR_{SR} and fSR_3OfA. Total target and OAR doses in the simulated treatment courses were assessed by accumulation of the 35 simulated fraction doses. Dose accumulation was performed using the non-rigid registration framework developed by Vasquez Osorio et al. [41,42], which determines the deformation vector field between contours on rCT and pCT.

For CTVs, the near minimum $V_{95\%}$ and the near maximum $V_{107\%}$ of the CTVs per patient in the 25 simulated treatments were compared for the treatment strategies. The near minimum was defined as the 90% worst case DVH value in the 25 simulated treatment. This value was obtained per patient by sorting the obtained DVH parameters in the 25 simulated treatments from best to worst, and performing a linear interpolation between the 22nd and 23rd value. The number of simulated treatments that complied with clinical constraints in the PL strategy were also compared between patients between treatment strategies.

For OARs, the risk of xerostomia and dysphagia, for both grade $\geq$ II and grade $\geq$ III complications was evaluated using the models in the Dutch National Indication Protocol [32]. NTCPs were computed in the 25 simulated treatments, and the average NTCP in the simulated treatments were compared between the different treatment planning strategies.

Statistical significance of dosimetric differences between treatment strategies were assessed using the Wilcoxin Signed-Rank test ($\alpha < 0.05$).

Results

In the PL approach, the 0, 1, 2, 3 and 5 mm SR library treatment plans were selected in 6%, 31%, 30%, 7%, 25% of the fractions, respectively. In 13% of the fractions, for 7 unique patients (Patients 1, 2, 7, 9, 11, 12 and 15) had one or two CTs for which none of the library treatment plans met the selection constraints and the 5 mm plan was selected (Table 2).

Fig. 1 shows the increase in the near minimum $V_{95\%}$ and $V_{107\%}$ of the CTVs per patient for $fSR_{0\text{-}5}$, and the corresponding near minimum for the PL strategy and fSR_3OfA. The corresponding statistical significance between PL and all evaluated strategies can be found in Appendix C. The near minimum of the CTV_{7000} $V_{95\%}$ in the PL strategy was 98.8% ± 1.0% (mean ± SD), compared to 98.7% ± 1.7% for fSR_3 (p = 0.89) and 99.2 ± 0.7% for and fSR_3OfA (p = 0.05). The near minimum $V_{95\%}$ of the CTV_{5425} in the PL strategy was 99.1% ± 0.5%, compared to 99.3% ± 0.8% for fSR_3 (p = 0.25) and 99.5 ± 0.5% for fSR_3OfA (p = 0.05). There were no statistically significant differences in near maximum $V_{107\%}$ between PL and fSR_3 and fSR_3OfA (p = 0.11 and p = 0.11).

Fig. 2 shows the increase in NTCP from a 0 to 5 mm fixed SR, and the corresponding NTCPs for the PL and fSR_3OfA strategies. The patient average increase in NTCP per mm SR in $fSR_{0\text{-}5}$ was 1.8 ± 0.8%-point for xerostomia grade $\geq$ II and 1.5 ± 1.0%-point for dysphagia grade $\geq$ II (Fig. 3). For some patients, for example Patient 3, the NTCP increase per mm SR was relatively large, resulting in a relatively large benefit from using smaller SR with the PL. NTCP differences for the 5 patients that received a plan adaptation (1, 7, 10, 12 and 15) between fSR_3OfA and fSR_3 were minor.

Table 2
Selected library treatment plans for each of the repeat CTs (rCTs). Plans indicated with an asterisk did not meet the target selection criteria, resulting in a selection of the library treatment plan with the largest (5 mm) setup robustness setting.

	rCT1	rCT2	rCT3	rCT4	rCT5	rCT6
Patient 1	0 mm	1 mm	5 mm*	5 mm*		
Patient 2	2 mm	5 mm*	1 mm	1 mm	1 mm	1 mm
Patient 3	2 mm	3 mm	2 mm	2 mm	1 mm	
Patient 4	2 mm	2 mm	2 mm			
Patient 5	0 mm	2 mm	2 mm	1 mm	1 mm	
Patient 6	1 mm	2 mm	2 mm	2 mm	5 mm	
Patient 7	2 mm	3 mm	5 mm	5 mm*		
Patient 8	1 mm	3 mm	2 mm			
Patient 9	1 mm	2 mm	5 mm*	5 mm*		
Patient 10	0 mm	1 mm	1 mm	5 mm	3 mm	
Patient 11	3 mm	2 mm	2 mm	5 mm*		
Patient 12	5 mm*	1 mm	5 mm	5 mm		
Patient 13	2 mm	1 mm	1 mm	1 mm	1 mm	1 mm
Patient 14	1 mm	2 mm	2 mm	1 mm	0 mm	
Patient 15	5 mm	5 mm	5 mm	5 mm*		

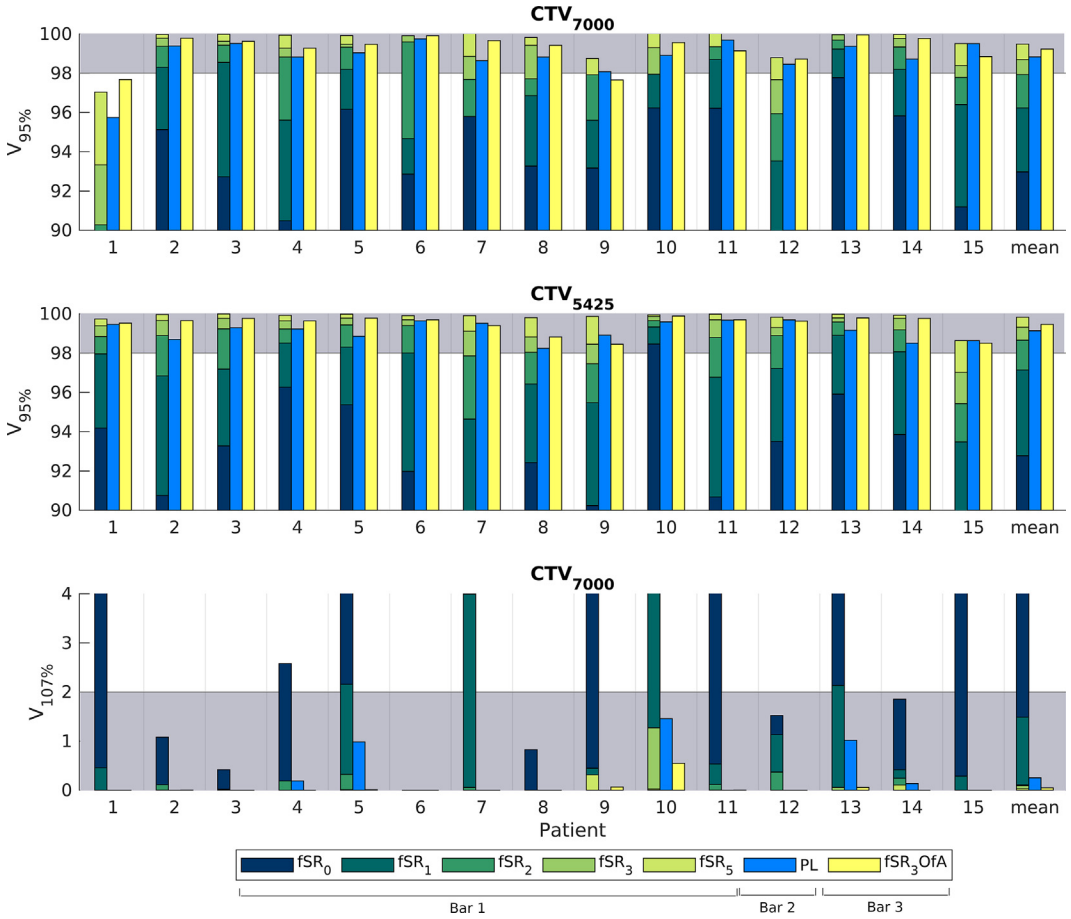

Fig. 1. The near minimum $V_{95\%}$ of CTV_{7000} and CTV_{5425}, and $V_{107\%}$ of CTV_{7000} per patient with fixed setup robustness settings ($fSR_{0\text{-}5}$), the plan library strategy (PL) and for the offline adaptive scheme with 3 mm setup robustness settings (fSR_3OfA). Areas that comply with clinical treatment constraints ($V_{95\%}$ > 98% and $V_{107\%}$ < 2%) are plotted in grey. Near minimum values were obtained by taking the 90% of the distribution in the 25 simulated treatments per patient. Note that only patients 1, 7, 10, 12 and 15 had an offline adaptive plan.

Fig. 3 shows differences between fSR_3 and fSR_3OfA and the PL strategy in NTCPs and number of simulated treatments that complied with clinical target constraints ($V_{95\%}$ > 98% for both CTVS & $V_{107\%}$ < 2% for CTV_{7000}) per patient. Compared to fSR_3, the PL approach resulted in NTCP improvements for 11/15 patients for xerostomia and 10/15 for dysphagia. For 6/15 patients, the risk of xerostomia and/or dysphagia ≥ grade II could be reduced by > 2%. The mean xerostomia ≥ grade II & III improvement with

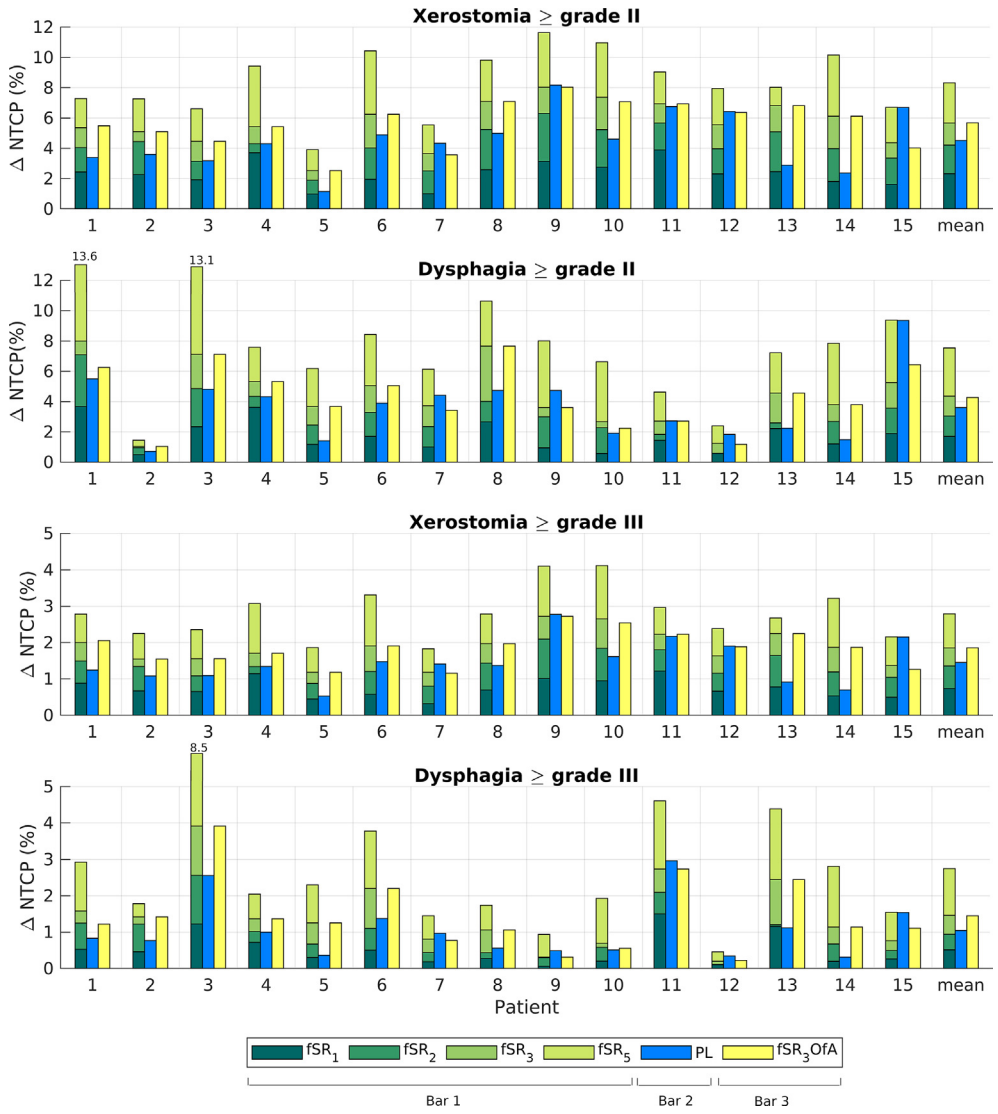

Fig. 2. Normal tissue complication probability (NTCP) difference with 0 mm fixed setup robustness (fSR_0) for 1–5 mm fSR ($fSR_{1\text{-}5}$), plan library (PL) strategy and offline adaptive (OfA) fSR_3OfA strategy. Note that only patients 1, 7, 10, 12 and 15 had an offline adaptive plan.

the PL was 1.2 ± 1.7%-point & 0.4 ± 0.6%-point (p = 0.02 for both). The risk of dysphagia ≥ grade III was also significantly improved with 0.4 ± 0.6%-point (p = 0.03). For the 4 patients with NTCP increase in the PL strategy (Patients 7, 9, 12 and 15), adherence to clinical coverage constraints was improved instead (Fig. 2).

Compared to fSR_3OfA, the PL approach resulted in significantly improved NTCP for xerostomia ≥ grade II & III (p = 0.02 for both), and dysphagia grade ≥ III (p = 0.03). For 9/15 patients (13, 14, 8, 6, 10, 5, 6, 4 and 2), the PL approach resulted in NTCP gain at limited costs in adherence to target constraints. For one patient (9), the PL approach resulted in gain in adherence to clinical target constraints at the cost of NTCP. For 4/15 patients (1, 7, 12 and 15), there was a loss in NTCP in combination with a loss in adherence to target constraints or no difference in adherence to target constraints.

Discussion

In this study, we proposed and investigated the use of online adaptive IMPT based on patient-specific PLs. The PLs contained robustly optimized plans with different SR settings. To the best of our knowledge, this is the first study that presents a PL approach with the aim to develop practically feasible online adaptive strategy for proton therapy. The presented PL strategy is an alternative to online re-optimization and selects suitable SR settings for the anatomy of the day. For every fraction, a plan is selected based on recomputed dose to the CTV on a daily CT.

The proposed PL approach outperformed treatment planning with a fixed 3 mm SR plan (fSR_3), by either 1) reducing NTCP for similar adherence to CTV constraints or 2) improved CTV coverage by more consistent adherence to constraints. Compared to an offline adaptive scheme (fSR_3OfA) based on the clinical decision to replan, the PL resulted in overall significantly improved NTCPs. For selected patients, NTCPs was improved at limited costs in CTV coverage, while for other patients CTV coverage was improved with fSR_3OfA.

The PL and offline replanning approach could be combined by extending the PL with offline replans. This could further improve CTV and OAR doses in the presence of systematic changes in patient geometry. Furthermore, the selected plans from the library could be used as an indication to trigger the addition of offline replans to the library. For example, the selection of 5 mm treatment plans for multiple fractions in a row could be used to trigger the offline generation of new plans. As the proposed PL strategy,

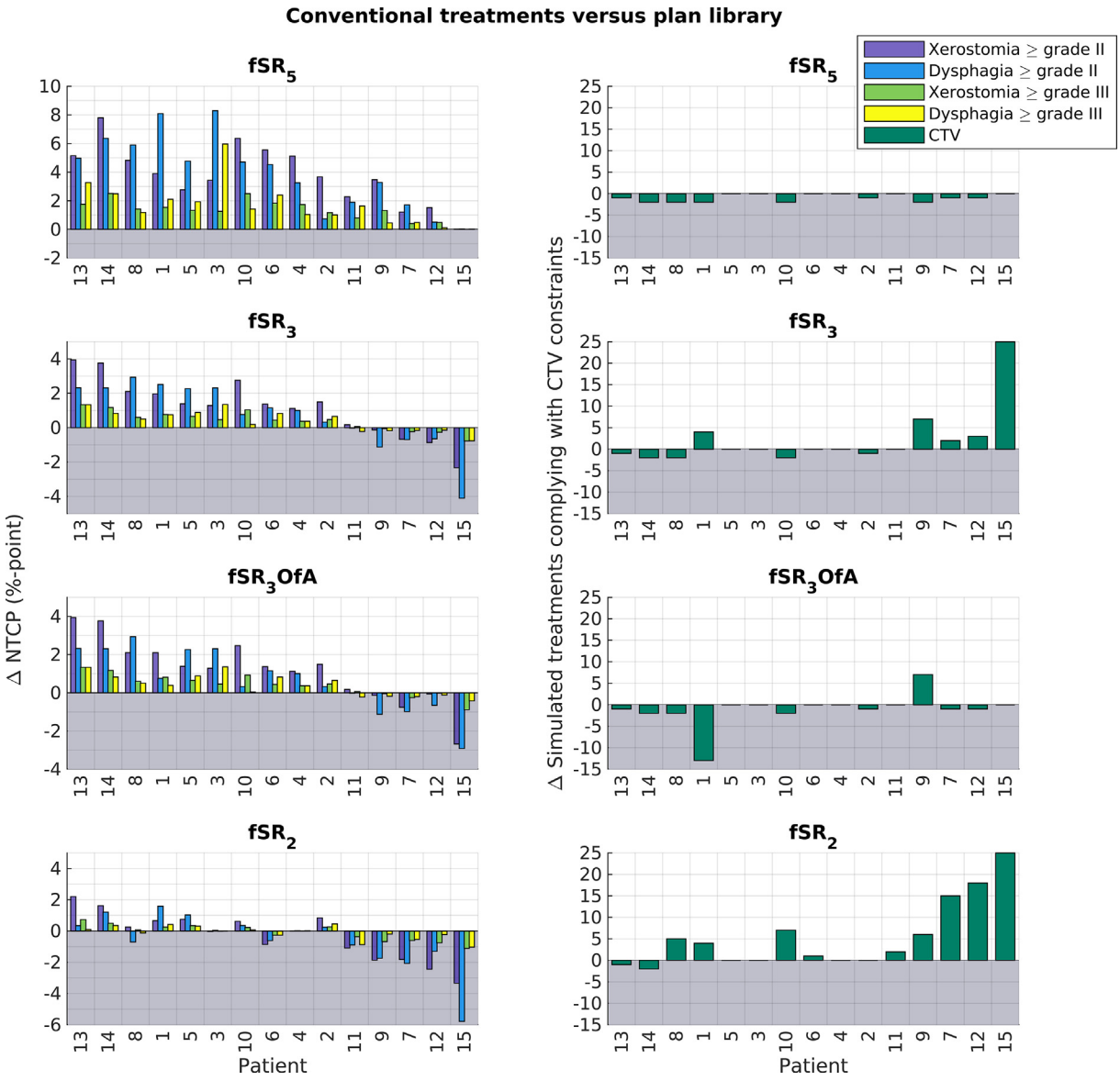

Fig. 3. Differences between the plan library (PL) approach and treatments with a fixed setup robustness setting ($fSR_{2,3,5}$) and the offline adaptive strategy (fSR_3OfA). Left panels: differences in normal tissue complication probabilities (NTCP) for xerostomia and dysphagia ≥ grade II and grade ≥ III. Right panels: differences in numbers of simulated treatment courses out of 25 that complied with all clinical CTV constraints (both CTV $V_{95\%}$ > 98% and CTV_{7000} $V_{107\%}$ < 2%). In non-shaded areas, the PL strategy is favorable. Patient order was based on NTCP gain for the PL strategy compared to fSR_3.

offline plan adaptation is also a time consuming procedure, disturbing the clinical workflow.

The advantage of the proposed online PL compared to online re-optimization strategies is that it can improve NTCPs without fundamental changes in the treatment planning procedure and technique. In contrast to online re-optimization, treatment planning and plan-QA can be performed using regular procedures with the PL strategy. Furthermore, edited contours of the OARs are not needed for online adaptation with the PL strategy. Other studies [15,43] have compared their online re-optimization approach with conventional robust treatment planning and also found significant dosimetric improvements. Future work should investigate whether treatment quality using our PL strategy can be further enhanced by online adaptive re-optimization strategies.

A different strategy to mitigate the effects of patient geometry variation is anatomical robust optimization, where multiple CTs are optimized under perturbed situations, thus taking into account variations of the patient geometry during treatment plan optimization. While target coverage was shown to be superior to using isotropic SR settings [14,44], this came at the cost of an increase in dose to the OARs. The advantage of the proposed PL strategy is that instead of increasing robustness to account for possible daily geometries, daily geometrical differences can be anticipated with a suitable isotropic SR setting. Ideally, the PL would be extended with multiple treatment plans optimized for variations of the patient geometry.

A limitation of this study is the use of 3–6 rCTs instead of daily imaging. As a result, random anatomical changes in the rCTs were more systematic during the simulations, possibly leading to increased systematic underdosage and therefore underestimation of true target coverage. Also, by assuming that the out-of-room rCTs reflected the treatment position at the gantry, potential differ-

ences with actual treatment position were neglected. The availability of only 3–6 rCTs impacted the evaluation of the offline adaptive schedule, as we simulated that the offline replans were only used from the next CT onwards. Therefore, clinically triggered plan adaptations on the last CT could not be taken into account. Also, plans were only adapted after 7–9 fractions, which may not reflect true clinical plan adaptation time.

The use of a PL would lead to an increased workload compared to the current conventional clinical procedures in generating the PL, performing offline plan QA and online plan selection. The aim of this study was to evaluate the potential dosimetric improvement of the proposed PL strategy. The required extra treatment time and resources were not assessed. Online plan selection in our study requires a daily in-room CT with CTV contours and forward dose computations. The proposed workflow could be feasible in terms of adaptation time, but can still be improved. Plan selection in the proposed workflow using daily CTs requires an in-room CT scanner on-rails (available at HollandPTC). The clinical feasibility of the PL strategy could be improved if it was based on daily CBCTs. This would both speed up the workflow, and minimize patient radiation exposure. Strategies to use the CBCT imaging data for dose computation have been presented and evaluated [45–47]. Manual contour adjustments after propagation could take a radiation oncologists around 10 minutes. The clinical feasibility in terms of online adaptation time could potentially be improved by the use of automatically propagated contours, which would require further investigation. Forward dose computations can be performed within time constraints of an online setting, as currently clinically available software can compute dose within < 10 s.

Future improvements of our work include alterations in the online plan selection procedure. First of all, the plan selection criteria in this work were tweaked for the studied patient group. Before clinical introduction of the strategy, selection criteria should be validated on an another dataset. Second, in our study, plan selection was based on nominal dose to the rCT. The behavior of the dose distribution in the presence of uncertainties was not taken into account during plan selection, nor was the dose in the previous fractions. To improve plan selection strategy, a future study could explore the use of more sophisticated selection criteria, e.g., taking into account uncertainties and using accumulated dose. Lastly, in this study we used an automatic dosimetric trigger for plan selection. In a clinical workflow, we believe that in a clinical workflow a radiation oncologist or trained RTT should at least verify the plan selection process.

Other future improvements of our PL strategy could be with regards to patient selection and inclusion. First of all, patients could be pre-selected based on potential NTCP improvements. NTCP improvement for a patient using a PL does not only depend on the selected SR setting, but also the increase in NTCP per mm SR (Fig. 2). This dependence can be evaluated during PL generation, and patients that are likely to benefit from the PL approach could be selected. Second, for a subset of H&N patients where the target is close to sensitive serial OARs, robust target coverage needs to be sacrificed in order to comply with clinical constraints on serial OARs. These patients were excluded for this study but make up a significant part of the H&N patient population. Daily plan selection criteria for these patients should be based on a combination of dose to serial OARs and target.

In conclusion, the presented online adaptive PL approach resulted in NTCP reductions with adherence to target constraints similar to treatment with a fixed SR plan. Furthermore, this strategy improved adherence to target constraints for selected patients, reducing the need for ad hoc re-planning. Target coverage can be improved by offline replanning. Using this practical PL approach, NTCPs can be improved while the issues of online reoptimization times and plan QA can be avoided.

Disclosures

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Conflict of Interest

None declared.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.09.011.

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