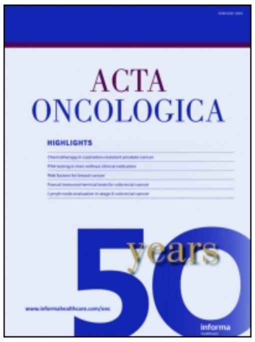

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ORIGINAL ARTICLE

Plan-library supported automated replanning for online-adaptive intensity-modulated proton therapy of cervical cancer

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ABSTRACT

Background: Intensity-modulated proton therapy is sensitive to inter-fraction variations, including density changes along the pencil-beam paths and variations in organ-shape and location. Large day-to-day variations are seen for cervical cancer patients. The purpose of this study was to develop and evaluate a novel method for online selection of a plan from a patient-specific library of prior plans for different anatomies, and adapt it for the daily anatomy.

Material and methods: The patient-specific library of prior plans accounting for altered target geometries was generated using a pretreatment established target motion model. Each fraction, the best fitting prior plan was selected. This prior plan was adapted using (1) a restoration of spot-positions (Bragg peaks) by adapting the energies to the new water equivalent path lengths; and (2) a spot addition to fully cover the target of the day, followed by a fast optimization of the spot-weights with the reference point method (RPM) to obtain a Pareto-optimal plan for the daily anatomy. Spot addition and spot-weight optimization could be repeated iteratively. The patient cohort consisted of six patients with in total 23 repeat-CT scans, with a prescribed dose of 45 Gy(RBE) to the primary tumor and the nodal CTV. Using a 1-plan-library (one prior plan based on all motion in the motion model) was compared to choosing from a 2-plan-library (two prior plans based on part of the motion).

Results: Applying the prior-plan adaptation method with one iteration of adding spots resulted in clinically acceptable target coverage ($V_{95\%} \geq 95\%$ and $V_{107\%} \leq 2\%$) for 37/46 plans using the 1-plan-library and 41/46 plans for the 2-plan-library. When adding spots twice, the 2-plan-library approach could obtain acceptable coverage for all scans, while the 1-plan-library approach showed $V_{107\%} > 2\%$ for 3/46 plans. Similar OAR results were obtained.

Conclusion: The automated prior-plan adaptation method can successfully adapt for the large day-to-day variations observed in cervical cancer patients.

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Introduction

Highly localized dose deposition is possible in intensity-modulated proton therapy (IMPT) using the characteristic Bragg peak. At the same time, this treatment modality is sensitive to inter-fraction variations, including density changes along the pencil-beam paths and variations in organ-shape and location [1,2].

Large day-to-day variations can be seen in the shape and position of the cervix-uterus, mostly due to changes in filling of bladder, rectum and sigmoid. Displacements of the tip of the uterus of more than 3 cm between an empty-bladder and a full-bladder anatomy are common. In photon beam radiotherapy, a plan-of-the-day approach has been clinically implemented in several centers, in which a daily image is used to select the best fitting treatment plan from a plan-library [3,4].

For cervical cancer IMPT, such an approach has been investigated by Schoot et al. [5]. The cervix-uterus positions of a full- and empty-bladder CT scan were used to create an internal target volume (ITV) encompassing all possible positions. This ITV was divided into subITVs with which a patient specific plan-library was generated. All library plans were robustly optimized using 8 mm setup errors and 3% range errors. For each simulated fraction, the library plan encompassing the daily CTV was selected, and recalculated on the daily anatomy without further (re-)optimization. Despite the generous robustness settings, the selected plan resulted in inadequate CTV coverage in about 10% of the repeat-CT scans, due to ‘substantial deviating anatomy compared to the pretreatment derived full range ITV’ [5]. This shows that when the daily anatomy greatly deviates from the pretreatment observed motion, using a plan-library with robust treatment plans is insufficient to guarantee target coverage.

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Supplemental data for this article can be accessed here.

In this study we therefore propose to automatically adapt the treatment plan that is selected from the plan-library using our automated plan adaptation method developed for prostate cancer in previous work [6]. In this proposed prior-plan strategy, the plan selected from a library of prior plans is adapted by an energy adaptation of the pencil-beams, followed by adding spots and a weight optimization using the reference point method (RPM) using automatically tuned RPM-parameters. Outcomes were compared to forward dose calculation of the prior plans on the repeat-CT scans (no replanning), and to full, time-consuming multi-criteria optimizations for the daily scans (benchmark). To investigate the effect of using a prior plan as a warm-start for optimization, outcomes were also compared to a time-constrained non-prior-plan strategy in which a new plan is generated from scratch for the daily scans.

Material and methods

Patient data

This study included data of six patients with locally advanced cervical cancer selected from an institutional review board approved prospective study designed to investigate inter-fraction motion in cervical cancer patients. For every patient, a full- and empty-bladder CT scan was acquired pretreatment as well as four weekly repeat-CT scans, resulting in a total of 23 repeat-CT scans. More detailed background of the patient data can be found in the Supplementary Materials.

Treatment planning volumes and prescription

The goal was to obtain clinically acceptable daily treatment plans for the repeat-CT scans. In the foreseen online-adaptive workflow, we assume that the structures are daily segmented automatically or with minimal user interaction. To account for intra-fraction uncertainties and inevitable uncertainties in the structure segmentation of the adaptive workflow, the daily targets were expanded with a margin: a PTV_{OAPT} (PTV Online-Adaptive Proton Therapy) was created by adding a 5-mm margin around the primal CTV and a 2-mm margin around the nodal CTV [7,8]. Prescribed dose to the PTV_{OAPT} was set to 45 Gy(RBE), using an RBE of 1.1, which was delivered by four beams (0°, 90°, 180°, and 270°).

The automated adaptive treatment planning method

The proposed strategy starts by selecting the best prior plan from a plan-library. The spot-positions are then restored by adapting the energy of each spot to the new water equivalent path length (WEPL). To adapt for changes in shape and location of the target, 3000 new spots are added prior to the optimization with the RPM. The combination of the spot addition and spot-weight optimization can be repeated. In this study, we evaluated using the spot-position restoration in combination with zero (i.e., only optimize the restored spots), one and two iterations of adding spots and spot-weight optimization. Supplementary Figure S1 of the Supplementary Materials illustrates the workflow of the proposed strategy.

A detailed description of this approach is given in [6]. The two extensions of the existing method, namely the library of prior plans and RPM-parameter tuning, are discussed below.

Plan-library generation for the prior-plan strategy

Due to potentially large day-to-day variations in the shape and location of the cervix-uterus, prior plans generated solely on either the full- or empty-bladder CT scan will likely result in insufficient spot coverage for the observed target deformations in the repeat-CT scans. For this reason, an in-house, non-rigid registration was used to derive for each patient a motion model describing the cervix-uterus shape for every possible bladder volume [4]. Using this pretreatment established motion model we created a 'Complete ITV' including all observed motion, as well as a 'Full' and 'Empty' subITV, focusing on parts of the observed motion. The 'Empty ITV' ranges from the cervix-uterus corresponding to the empty-bladder to the cervix-uterus corresponding to a 'half-full-bladder' structure and the 'Full ITV' ranges from the cervix-uterus corresponding to this half-full-bladder to the cervix-uterus corresponding to the full-bladder. Supplementary Figure S2 of the Supplementary Materials shows an example of the three ITV structures in the sagittal view.

We investigated two library types for the prior-plan strategy:

- 1-plan-library: One prior plan, based on the 'Complete ITV'.
- 2-plan-library: Two prior plans, based on the 'Full' and 'Empty' subITVs.

All prior treatment plans were generated based on a PTV_{Prior} which encompassed the Complete ITV or Full/Empty subITV enlarged with a 5-mm margin and the nodal CTV enlarged with a 4-mm margin. Anatomical differences not accounted for by the PTV_{Prior} are expected to be handled by adding new spots during replanning.

The prior treatment plans were generated using 'Erasmus-iCycle', our in-house developed treatment planning system for fully automated plan generation, combined with the 'Astroid' dose engine. The optimization iteratively adds and removes spots to the target, without time restrictions, see [9–14] and the Supplementary Materials for more details. It is important to note that these prior plans were not intended as the definitive treatment plan, but serve as a warm-start for daily replanning.

Library plan selection strategies

In the case of a 2-plan-library, a selection had to be made between the two prior plans in the library. Traditionally this is done by comparing the bladder volume to a half-full-bladder structure. In this work we selected based on the daily anatomy and the restored spot-positions, without assuming the cervix-uterus motion to be linked to bladder filling. The percentages of the total spots of the library plans that ended up in the daily target region after spot-position restoration were compared. If the difference was more than 1%-point, the plan with the highest percentage was selected as prior. If not, both plans fit the daily anatomy equally well. In that case, the plan with the most spots ending up in the daily target region after restoration was selected as prior.

RPM-parameter tuning

The RPM is used in this study to automatically optimize the spot-weights in a single optimization. The output is a Pareto-optimal solution, with objective tradeoffs in line with the original (i.e., prior) plan. To get these tradeoffs, the required RPM-parameters were automatically tuned. As the results of the prior-plan adaptation method might depend on the RPM-parameters, three-fold cross validation was applied. For each fold, two different patients were used for parameter tuning. The planning strategies using the found parameters were tested on the other four patients of each fold. Evaluation was done on all folds simultaneously: i.e., on 46 plans (two plans for each scan). More information on the RPM, the RPM-parameter tuning and the individual folds can be found in the Supplementary Materials and [6,15–19].

Comparison and evaluation of the methods

In this study, we benchmarked the results of the prior-plan strategy against fully multi-criteria optimized plans. These benchmark plans were generated for each fraction on the PTV_{OAPT} with the same approach as was used for the prior plans (above).

Besides the time-consuming full multi-criteria benchmark optimization, we investigated a replanning strategy that does not require a prior plan. New spots are placed in the target region, which are then optimized using the RPM. Two approaches for the non-prior-plan strategy were investigated:

- New-Spots-E3: New spots were positioned in a regular grid, using a 5 mm lateral spacing and an energy spacing three times the longitudinal width of the Bragg peak (at 80% of the peak height).
- Sampled-New-Spots-3x: New spots were iteratively added as was done for the benchmark and prior plans. To limit the calculation times, the optimization was stopped after three iterations.

We compared the prior-plan strategy to the non-prior-plan strategy to see whether the use of a prior plan as a warm-start is beneficial for either plan quality or calculation time. More details on the non-prior-plan strategy approaches can be found in the Supplementary Materials. Other strategies, energy spacings and number of iterations are also reported there.

Table 1 gives an overview of the different methods which were included in the evaluation.

For each repeat-CT scan, the dose distributions of all strategies (forward calculation of the prior, prior-plan strategy, non-prior-plan strategy and benchmark) were checked to see whether they fulfilled the planning criteria ($V_{95\%} \geq 95\%$ and $V_{107\%} \leq 2\%$) for the PTV_{OAPT}. In addition, all dose distributions were visually checked for hot-spots inside and outside the target volumes.

For the PTV, we report the $V_{95\%}$ and $V_{107\%}$. For rectum, bladder and bowelbag, we report the $V_{30Gy(RBE)}, D_{mean}$ and D_{max} and, for the sigmoid, femoral heads and whole body (patient) we report the D_{max}.

All calculations were performed on a dual Intel Xeon E5-2690 server.

Results

Results for the targets

All prior plans achieved the $V_{95\%}$ and $V_{107\%}$ requirements for the respective PTV_{Prior} volumes. Table 2 shows for each treatment strategy the number of plans that met the target demands. It can be seen that forward calculation of the prior plans, i.e., without replanning, always resulted in inadequate target coverage. Replanning using the prior-plan approaches without the addition of new spots (0×) achieved sufficient $V_{95\%}$ values, but too high $V_{107\%}$ values. Adding spots once (1×) yielded acceptable target coverage for more than 80% of the plans. Acceptable coverage was only obtained for all plans with the 2-plan-library-2× approach.

For the non-prior-plan strategy, Table 2 shows that while using a fine regular grid (New-Spots-E3) always resulted in acceptable target coverage, iteratively sampling new spots (Sampled-New-Spots-3×) achieved the demands in only 84% of the plans.

Table 1. Overview of the different treatment plans that are compared.

Method	Explanation
No replanning: Forward dose calculation of prior plan on daily CT	Prior treatment plan selected from a plan-library, recalculated for each aligned repeat-CT scan as if it would have been delivered to that scan. Note that as these prior plans were not intended for treatment, the results are only shown to illustrate that replanning is required.
1-plan-library / 2-plan-library: Prior-plan strategy	Prior treatment plan selected from a plan-library, adapted for each repeat-CT scan by an energy layer constrained WEPL correction followed by zero, one or two (-0×, -1×, -2×) iterations of spot addition (adding 3000 spots per iteration) and RPM optimization.
Sampled-New-Spots-3×/New-Spots-3×: Non-prior-plan strategy	Treatment plan generated by placing only new spots in the target region and using the RPM to optimize the spot intensities on the PTV_{OAPT} for each repeat-CT scan. Spots were either positioned in a regular grid, or randomly selected from a very fine regular grid using a limited number of iterations.
Benchmark	Treatment plan optimized from scratch using 'Erasmus-iCycle' on the PTV_{OAPT} for each repeat-CT scan. Currently the best achievable plan if no time constraints would apply. This plan was included as a benchmark of obtainable plan quality.

Results for the OARs

In Figure 1, the OAR results obtained using the 1-plan-library-2× approach and the 2-plan-library-2× approach are compared to the OAR results of the benchmark plans. The highest prioritized criteria (D_{max}) deteriorated less than 5 Gy(RBE) compared to the benchmark plans, where some resulted in even lower doses (bowelbag, sigmoid D_{max}). For the 2-plan-library-2× approach, the largest deviation (+14%-point) was seen for the rectum $V_{30Gy(RBE)}$, obtaining a value of 63%, where the benchmark plan had a value of 49%.

In Figure 2, the OAR results of the best approach of the prior-plan strategy (2-plan-library-2×) and the two approaches of the non-prior-plan strategy are compared to benchmark. Similar OAR results were obtained for the 2-plan-library-2× and the New-Spots-E3 approaches, while the Sampled-New-Spots-3× approach showed slightly larger deviations from benchmark.

Calculation times

Generating the library of prior plans took on average 1.5 h per plan, including dose calculation. Table 2 shows the total calculation times required for all treatment strategies, excluding the final dose calculation. In the prior-plan strategy, the spot-position restoration step took on average 5.9 seconds (range 4.4–7.4) per restored plan. After restoration, the dose deposition matrix was recalculated in on average 1.2 min (1.0–1.4). Without the addition of spots, the RPM spot-weight optimization took on average 28.0 s (19.7–54.8). Adding new spots and calculating their dose deposition matrices was completed in on average 1.4 min per iteration (0.9–2.5). With the addition of new spots, the average calculation time of the RPM spot-weight optimization increased to 1 min (0.6–1.7) per iteration.

Table 2. For each treatment strategy, the number of plans that meet the prescribed target demands.

	$V_{95\%} \geq 95\%$ & $V_{107\%} \leq 2\%$	Calculation times (min.) mean (min–max)
1-plan-library No replanning	0/46	–
2-plan-library No replanning	0/46	–
1-plan-library-0×	2/46	1.9 (1.6–2.4)
2-plan-library-0×	0/46	2.1 (1.7–2.5)
1-plan-library-1×	37/46	4.2 (3.2–5.2)
2-plan-library-1×	41/46	4.2 (3.4–5.4)
1-plan-library-2×	43/46	6.4 (5.1–8.3)
2-plan-library-2×	46/46	6.6 (5.3–8.4)
Sampled-New-Spots-3×	39/46	7.1 (5.7–8.4)
New-Spots-E3	46/46	40.7 (25.0–78.4)
Benchmark	46/46	56.4 (25.3–85.1)

The last column shows for each treatment strategy the total calculation time excluding the final dose calculation.

Discussion

In this study, we combined a plan-library approach with a previously developed RPM adaptive method in a prior-plan strategy. The combination of selecting a prior plan and adding new pencil-beams could account for density changes along the pencil-beam paths and large inter-fraction shape changes of targets and OARs. Clinically acceptable treatment plans were obtained for all plans when using the 2-plan-library-2× approach. One iteration of spot addition was already sufficient for more than 80% of the plans.

Plans were considered acceptable if they achieved $V_{95\%} \geq 95\%$ and $V_{107\%} \leq 2\%$. As all discussed strategies were completely automated, these demands were strictly checked, even though slight deviations might be clinically acceptable. The latter can be incorporated by automatically notifying the user when the plan is within a prescribed bandwidth of the demands.

Applying the prior treatment plans without replanning resulted in inadequate target coverage, while in [5], most scans obtained acceptable target coverage. The differences can be explained by the fact that our prior plans were not intended for actual dose delivery, but only as a warm-start

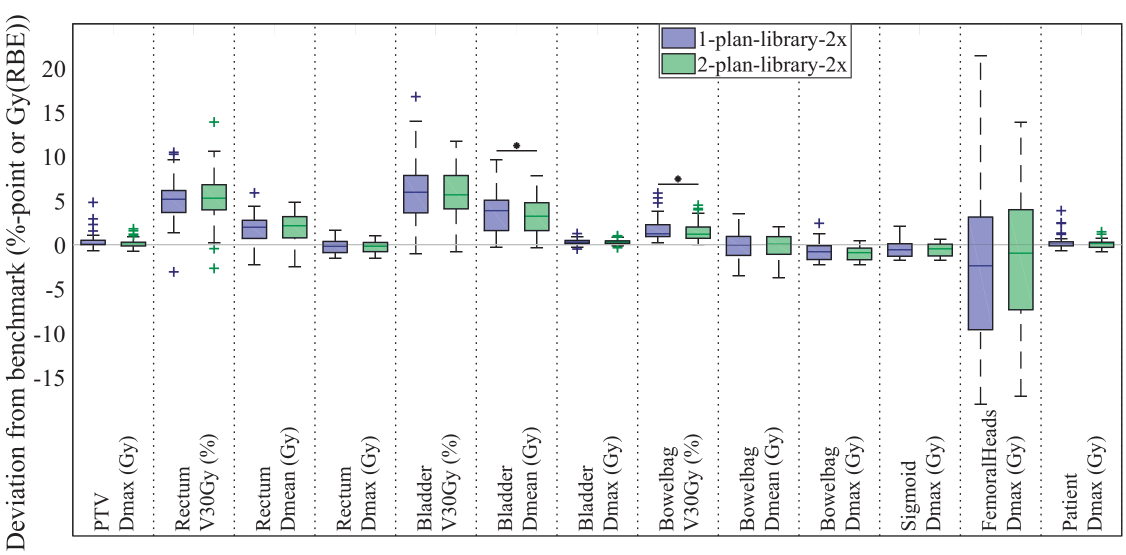

Figure 1. Boxplots depicting the OAR differences between the prior-plan strategies with two iterations of adding spots and benchmark. In blue, the prior-plan strategy is shown using the 1-plan-library approach and in green the 2-plan-library approach. Negative deviations depict scans for which the OAR value is lower in the RPM plan than in benchmark. Statistically significant differences (Wilcoxon signed-rank test, 1% significance level, $p < .01$) are indicated by asterisks.

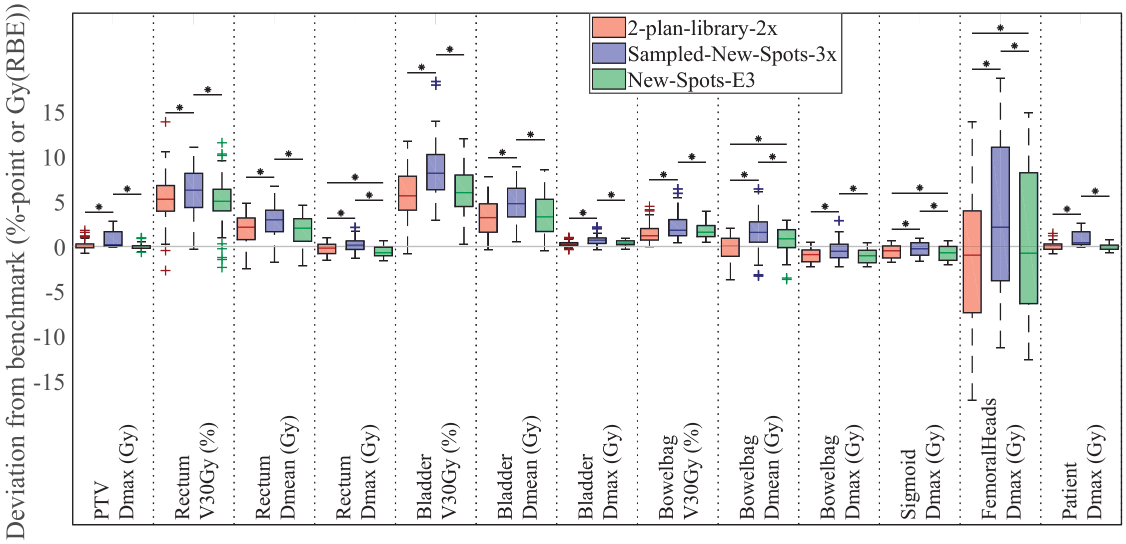

Figure 2. Boxplots depicting the OAR deviations from benchmark for the best prior-plan strategy approach and the non-prior-plan strategy approaches. In red the prior-plan strategy is shown using the 2-plan-library-2× approach, in blue the non-prior strategy using the Sampled-New-Spots-3× approach and in green the non-prior strategy using the New-Spots-E3 approach. Negative deviations depict scans for which the OAR value is lower in the RPM plan than in benchmark. Statistically significant differences (Wilcoxon signed-rank test, 1% significance level, $p < .01$) are indicated by asterisks.

for daily replanning. For this reason, no robustness was used in the optimization of the prior plans. In the Supplementary Materials, we show that robustness against uncertainties in stopping power prediction can be added at the cost of a limited increase in optimization time.

Comparing the 1-plan-library with the 2-plan-library approaches, Table 2 shows that the 2-plan-library performed slightly better, but the differences in success rate in terms of target coverage were small. Using a 2-plan-library-2× approach always resulted in clinically acceptable target coverage. Similar OAR results were obtained with the 1-plan-library-2× and the 2-plan-library-2× approaches (Figure 1).

We showed that a non-prior-plan strategy in which no warm-start is used can result in clinically acceptable treatment plans when sufficient spots are included. Figure 2 and Table 2 show that the plans from New-Spots-E3 obtain similar OAR results as the 2-plan-library-2× approach, while requiring over six times longer calculation times. This makes this option infeasible for online replanning. Although the New-Spots-Sampling-3× approach requires similar calculation times as the proposed prior-plan method with two iterations of spot addition, only 39/46 plans fulfilled the target demands (Table 2). To obtain good results for all plans would require more iterations of spot addition, again indicating that without a warm-start (i.e., a non-prior-plan approach) calculation times increase.

Several approaches of adaptive IMPT have been reported in the literature. An offline approach was proposed by Kurz et al., in which a new plan is generated to serve as an update for the next fraction [20]. One hour was required for deformable image registration (DIR), optimization and dose calculation. Adaptation reduced over-dosage in the targets and partially improved OAR sparing. Bernatowicz et al. compared dose restoration methods using new spots (no prior plan) aiming to restore a given reference dose distribution [21]. Without restoration less than 45% of the repeat-CT scans achieved adequate target coverage; with restoration this improved to 100%. The difference is that our method optimizes the dose distribution to the daily anatomy, while their restoration methods intend to only restore a prior dose distribution. Botas et al. [22] developed online-adaptation approaches based on cone beam CTs (CBCTs) in which only spots from the prior plan were used. A spot restoration was applied using DIR and, if necessary, this was followed by a weight tuning. Applying only a spot restoration was found to be insufficient; combined with a weight tuning acceptable results were obtained. Calculations were done using GPU-based Monte Carlo.

For conventional radiotherapy, the combination of a restoration followed by a weight optimization was reported by Ahunbay et al. [23]. Segment aperture morphing combined with segment weight optimization showed to improve target coverage and OAR sparing. Adaptation was possible in 10 min. Recently adaptive planning methods for the MR-linac have been described by Winkel et al. [24]. Two main categories of the adaptation methods are described as 'adapt-to-position' and 'adapt-to-shape'. Our replanning method would belong to the latter. Other centers have implemented a stereotactic MR guided adaptive workflow (SMART) [25–28]. Generating online-adaptive plans when target and OAR aims were not met resulted in adequate target coverage and better OAR sparing.

In this study, we decided to ignore the simultaneously integrated boost that is recommended in the EMBRACE II protocol. Including the boost would not alter the workflow. If more spots are needed to cover the boost this could slightly increase the calculation times. For the prior plan selection approach, a threshold of 1%-point was used for the initial selection criterion. While this setting is admittedly ad hoc, it demonstrated good results. Also, the proposed replanning methods currently add 3000 new spots to the optimization per iteration, which is the same number as was used in the optimization of the benchmark and prior plans. It is possible that using a different number in the replanning could result in acceptable results after fewer iterations. Fewer iterations might also be achieved by using a different beam setup (i.e., not 0°, 90°, 180°, and 270°), as other beam setups could be more robust against the daily anatomical variations. Finally, this proof of principle study was conducted on a small dataset consisting of six patients. Further investigation based on more data is necessary.

In conclusion, large day-to-day variations such as seen in cervical cancer radiotherapy can be accounted for in IMPT by applying a fast and automated prior-plan adaptation method. Selecting a prior plan from a plan-library, adapting its pencil-beams to the new WEPL, adding new spots and optimizing the spot-weights resulted in clinically acceptable treatment plans on daily anatomies. The use of a library of prior plans significantly reduced the optimization times to obtain clinically acceptable treatment plans.

Disclosure statement

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