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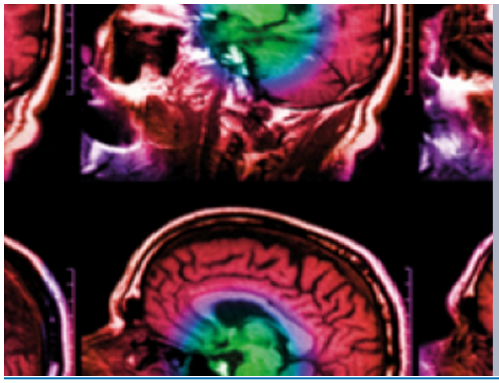

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Fast automated multi-criteria planning for HDR brachytherapy explored for prostate cancer

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Abstract

We developed a fast and fully-automated, multi-criteria treatment planning workflow for high dose rate brachytherapy (HDR-BT). In this workflow, the patient-CT with catheter reconstructions and dwell positions are imported from the clinical TPS into a novel system for automated dwell time optimisation. The optimised dwell times are then imported into the clinical TPS. The aims of automation were (1) planner-independent, enhanced plan quality, (2) short optimisation times.

Our in-house developed system for fully automated, multi-criteria external beam radiotherapy (EBRT) treatment planning (Erasmus-iCycle) was adapted for optimisation of HDR-BT dose distributions. The investigations were performed with planning CT scans with catheter reconstructions and delineations of twenty-five low- and intermediate-risk prostate cancer patients who were previously treated in our center with 4 × 9.5 Gy HDR-BT. Automatically generated plans (autoplans) were compared to the corresponding clinical plans. All evaluations were performed in the clinical TPS.

The requested 95% tumour coverage was obtained for all autoplans, while this was only observed in 23/25 clinical plans. All autoplans showed a consistent reduction of the $D_{1\%}$ for the highest prioritised OAR, the urethra. The average and maximum reductions were 6.3%-point and 12.1%-point of the prescribed dose, respectively. In addition, conformality of the autoplans was higher. The autoplans had slightly smaller delivery times. Autoplanning took on average 4.6 s, including computation of the dose kernels.

1. Introduction

Current high dose rate brachytherapy (HDR-BT) is based on interactive ('manual') treatment planning, which has similar shortcomings as in external beam radiotherapy (EBRT) planning: time-consuming, high workload, lack of consistency due to inter- and intraplanner variability, plan quality dependency on allotted planning time, and limited reproducibility of plans.

A technical challenge in brachytherapy planning is the usual prescription on dose-volume metrics, turning treatment planning into solving a non-convex problem. Existing investigated optimisation approaches include evolutionary optimisation, such as simulated annealing (Lessard and Pouliot 2001, Deist and Gorissen 2016, Cui *et al* 2018a) or particle swarm optimisation (Van der Meer *et al* 2018, Maree *et al* 2018), mixed integer programming (Gorissen *et al* 2013, Morén *et al* 2018), or approximation of the problem with convex cost-functions (Morén *et al* 2019). Evolutionary and mixed integer programming approaches are in general computationally intensive and lack (local) optimality measures, whereas convex approximations are not precise or do not fully explore the global search space.

Maree *et al* (2018) concluded that current clinical prostate HDR-BT treatment plans are not optimal as they are not on the Pareto frontier. Multi-criteria treatment planning can offer tools to improve HDR-BT treatment planning, e.g. by interactive navigation (Ruotsalainen *et al* 2010), fast Pareto-front generation for dwell times

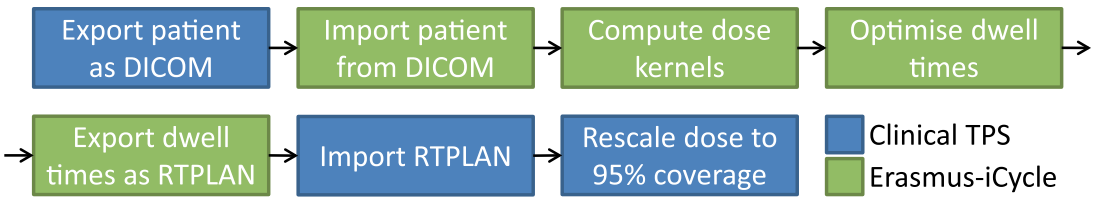

Figure 1. Flowchart of the steps used to enable optimisation of dwell times outside the clinical TPS. Blue boxes indicate steps in the clinical TPS environment, green boxes take place in Erasmus-iCycle.

only (Maree *et al* 2018, Cui *et al* 2018a), or with catheter optimisation as well (Yoo *et al* 2007, Van der Meer *et al* 2018).

In recent years we have developed Erasmus-iCycle for fully-automated, multi-criteria generation of EBRT treatment plans (Breedveld *et al* 2009, 2012). The system features so-called *a priori* multi-criteria optimisation (*a priori* MCO) (Breedveld *et al* 2019). As opposed to *a posteriori* MCO, with *a priori* MCO, a single high-quality plan is generated for each individual patient. In case of convex cost-functions, this plan is guaranteed Pareto-optimal. Many studies have demonstrated superiority of Erasmus-iCycle EBRT automatically generated treatment plans (i.e. *autoplans*) over manually generated clinical plans and the system is in routine use in our centre (Voet *et al* 2013, Heijmen *et al* 2018, Hussein *et al* 2018, Sharfo *et al* 2018).

In this paper we first adapted Erasmus-iCycle for dwell time optimisation in HDR-BT treatment planning. The system was then validated by comparing autoplans for prostate cancer patients with manually generated plans.

2. Methods and materials

2.1. Study design and autoplanning workflow

First, Erasmus-iCycle was adapted for brachytherapy autoplanning (details in section 2.3). Then, the system was configured for prostate cancer HDR-BT autoplanning with the same planning aims as used for the manual generation of clinical plans. Finally, for a group of patients, autoplans were generated and compared to the corresponding manually generated, clinically delivered plans. Plan comparisons were performed in the clinical TPS (Oncentra-Brachy TPS, version 4.5.1, Elekta AB, Stockholm, Sweden).

The workflow for generation of an autoplan and importing it into the clinical TPS is depicted in figure 1.

2.2. Patients and clinical planning

The investigations were based on post-implant CT-scans and corresponding clinical treatment plans of 25 low- and intermediate-risk prostate cancer patients that were previously treated in our center. HDR-BT was delivered as monotherapy in four fractions of 9.5 Gy in two consecutive days (Aluwini *et al* 2015). The target was defined as the prostate without margin expansions according to Aluwini *et al* (2012, 2015). In the remainder of this paper, doses such as $D_{1\%}$, and differences in these doses between the clinical and the autoplans are presented as percentages of the prescribed dose D^p.

Applied hard planning constraints for urethra, rectum and bladder, and planning objectives for the prostate and the urethra are summarised in table 1. The first priority objective was to achieve adequate target coverage within the imposed hard constraints, followed by minimisation of the near-maximum urethra dose ($D_{1\%}$) as the second priority.

The clinical plans were generated by expert planners using the clinical TPS, and reviewed by a radiation oncologist (SAL). Clinical planning was based on an IPSA (inverse planning by simulated annealing (Lessard and Pouliot 2001)) template, followed by manual fine tuning. On average 17 catheters were implanted (range 13–22) with 115 dwell positions (range 55–192).

2.3. Adaptation of Erasmus-iCycle for automated HDR-BT planning

To feature generation of HDR-BT plans, the software was adapted for optimisation of dwell times for a set of pre-selected dwell positions, instead of weights of pre-selected pencil beams in EBRT. For BT dose calculations, we implemented the HDR ^{192}Ir Flexisource dose kernel based on the TG-43 standard (Pérez-Calatayud *et al* 2012, Rivard *et al* 2004).

2.4. Erasmus-iCycle for prostate cancer HDR-BT

For automated treatment planning with Erasmus-iCycle, the clinical planning protocol is to be captured in a so-called wish-list, defining the optimisation protocol and containing the hard constraints and planning objectives

Table 1. Constraints and objectives in clinical planning in percentage of the prescribed dose D^p.

Constraints			
	Structure	Type	
	Urethra	Maximum $D_{1\%}$	120%
	Rectum	Maximum D_{1cc}	80%
	Bladder	Maximum D_{1cc}	80%
Objectives			
Priority	Structure	Type	Goal
1	Prostate (=PTV)	maximise $V_{100\%}$	95%
2	Urethra	minimise $D_{1\%}$	0

with assigned priorities and goal values (Breedveld *et al* 2009, 2012). While the planning constraints are never violated in plan generation, the goal values of the objective functions have to be met as well as possible, but will be attempted to supersede if feasible. Objective functions are sequentially optimised according to their priorities. After each objective function optimisation, a new constraint is added to the optimisation problem to ensure that the obtained function value is maintained while minimising lower priority objectives. The treatment site specific wish-lists are constructed in an iterative tuning process, using repetitive autoplanning for a small set of representative planning CT-scans (Heijmen *et al* 2018, Hussein *et al* 2018). Options for improving wish-lists in each iteration include adding or removing objective functions, changing priorities of objective functions, changing goal values, adding or removing constraints, etc. Although clinically delivered plans serve as an initial reference for wish-list generation, the final goal is always to supersede the clinical plan quality.

The wish-list for prostate HDR-BT is presented in table 2. The included constraints are in line with the clinical constraints (table 1), but for optimal steering in the autoplanning process, both for rectum and bladder a maximum dose constraint of 100% was added to avoid delivering excessively high doses to these OARs in very small volumes. In line with the clinical protocol, the first priority objective is obtaining 95% PTV coverage by the prescribed dose, followed by maximally reducing the near-maximum dose for the urethra as second priority. Instead of minimising $D_{1\%}$ directly, we use a different cost-function, which will be discussed in the next section. The two third-priority objectives then aim at reducing the high doses in rectum and bladder as much as possible, thereby also improving conformality.

To improve the optimisation performance, only points in the rectum and bladder up to 15 mm distance from the prostate were considered. Beyond this distance, the maximum expected dose was anyway much less than the constrained 80%. For the prostate, a resolution of 300 voxels cm^{-3} was used in the optimisations, while for the cropped rectum and bladder volumes 200 voxels cm^{-3} was used. For the urethra, all CT voxels were considered. Problem sizes are summarised in table 3.

2.5. Applied cost-functions and solver

Brachytherapy protocols are traditionally defined by dose-volume metrics. The V_{d^c} type of dose-volume metric (the volume that receives at least a certain dose d^c) can be written as an analytical function:

$$V_{d^c}^{exact}(d) = \frac{1}{m}\sum_{i=1}^{m} I_{d_i > d^c}(d_i), \tag{1}$$

with m the number of voxels in the volume, d_i the dose in voxel i, and I the indicator function that equals 1 if $d_i > d^c$ and 0 otherwise. This function is not continuous, not differentiable, and not convex, rendering it unsuitable for gradient-based solvers which are in general computationally efficient in finding an optimal solution. The Erasmus-iCycle solver is a full-Newton primal-dual interior-point solver, requiring continuous and twice differentiable cost-functions (Breedveld *et al* 2017). Therefore, equation (1) was not directly used for plan generation.

To work with dose-volume metrics as defined in table 2, the indicator function in (1) was substituted by a sigmoid function, as described in Alber and Reemtsen (2007), Breedveld *et al* (2017):

$$V_{d^c}^{approx}(d) = \frac{1}{m}\sum_{i=1}^{m} \frac{\left(\frac{d_i}{d^c}\right)^p}{1+\left(\frac{d_i}{d^c}\right)^p}, \tag{2}$$

where p determines the steepness of the sigmoid. This makes the function continuous and twice differentiable, but not convex. Extended functionality to encourage convergence to a suitable optimum for non-convex problems is part of the interior-point solver, see Benson *et al* (2002, 2004), Breedveld *et al* (2017). In this study p

Table 2. Applied wish-list for prostate HDR-BT. All dose levels are in percentage of D^p.

Constraints				
	Structure	Type	Limit	
	Urethra	Maximum $D_{1\%}$	120%	
	Rectum cropped	Maximum D_{max}	100%	
	Bladder cropped	Maximum D_{max}	100%	
	Rectum cropped	Maximum D_{1cc}	80%	
	Bladder cropped	Maximum D_{1cc}	80%	
Objectives				
Priority	Structure	Type	Goal	Parameters
1	Prostate	Maximise $V_{100\%}$	95%	Sufficient if 95% achieved
2	Urethra	Minimise LTCP	0	$d^c = 90\%, \alpha = -0.5$
3	Rectum cropped	Minimise $V_{70\%}$	0	
3	Bladder cropped	Minimise $V_{70\%}$	0	

Table 3. Numbers of dose optimisation points considered in the plan optimisations for prostate HDR-BT.

Structure	Mean	Range
Prostate	18 074	7750–29 610
Urethra	3916	1379–6875
Rectum cropped	2975	1241–5686
Bladder cropped	5800	1524–9680
Total per patient	30 765	16 634–47 424

was fixed at 100, while d^c was iteratively adjusted during the interior-point iterations to minimise the difference between V^{exact} and V^{approx}, aiming at an accuracy of 0.01%-point.

The D_x type of dose-volume metric (dose at a certain volume) cannot be written as an analytical function. For constraints, we can include those as the V_{d^c} version by using the equivalence:

$$D_x < d^c \iff V_{d^c} < x. \tag{3}$$

For D_x included as objective, no equivalent substitution exists. Therefore, for the urethra $D_{1\%}$ we used a different cost-function which reaches the same aim, i.e. minimising the near-maximum dose as far as possible. We used a variation of the logarithmic tumor control probability function (LTCP) (Alber and Reemtsen 2007) as a substitute. The LTCP is defined by:

$$\mathrm{LTCP} = \frac{1}{m}\sum_{i=1}^{m} e^{-\alpha(d_i - d^c)}. \tag{4}$$

As demonstrated by Rossi *et al* (2018), when using $\alpha < 0$, this cost-function is very effective in driving voxel doses d_i below the critical dose d^c.

2.6. Plan evaluations and comparisons

For the comparisons in the clinical TPS, we used the available highest precision dose-volume computation (200 000 sample points, 800 bins, and a high dose limit of 4 times the prescribed dose). Within these evaluation settings, both plans were rescaled to match either 95% target coverage or until one of the constraints was hit, followed by rounding dwell times to 0.1 s as requested by the TPS for clinical deliverability.

For the plan comparisons we used the clinical criteria as given in table 1. For comparing the delivery times, all times were rescaled to the same reference air kerma rate of the source.

In addition, conformality was evaluated using the COIN COnformality INdex (Baltas *et al* 1998), defined as:

$$\mathrm{COIN} = \frac{V_{\mathrm{PTV}\geqslant D^p}}{V_{\mathrm{PTV}}} \cdot \frac{V_{\mathrm{PTV}\geqslant D^p}}{V_{total\geqslant D^p}} \cdot \prod_{k=1}^{N_{\mathrm{OAR}}} \left[1 - \frac{V_{\mathrm{OAR}_k \geqslant d^{c,k}}}{V_{\mathrm{OAR}_k}}\right] \cdot 100, \tag{5}$$

with V_{PTV} the PTV volume, $V_{\mathrm{PTV}} \geqslant D^p$ the PTV volume receiving at least the prescribed dose D^p, $V_{total} \geqslant D^p$ the total patient volume receiving at least D^p, N_{OAR} the number of OARs (3 in this case), V_{OAR_k} the volume of OAR k, $d^{c,k}$ the critical dose for OAR k. For $d^{c,k}$, values as listed in table 1 were used (120%, 80% and 80% for the urethra, rectum and bladder, respectively). The three coefficients essentially reflect the coverage, conformality of D^p in

Table 4. Comparison of dosimetric plan parameters between clinical plans and autoplans. Doses for the OARs are given in percentages of D^p.

	Clinical plan		Clinical—auto		
Criterion	Mean	Range	Mean	Range	p-value
Prostate $V_{100\%}$ (>95%)	95.0%	94.4%–95.1%	−0.1%	−0.6%–0.1%	$p = 0.011$
Urethra $D_{1\%}$ (<120%)	112.8%	107.3%–120.0%	6.3%	1.0%–12.1%	$p < 0.001$
Rectum D_{1cc} (<80%)	70.2%	57.1%–79.6%	−1.2%	−6.9%–6.1%	$p = 0.087$
Bladder D_{1cc} (<80%)	68.5%	49.2%–79.3%	−5.4%	−10.8%–3.9%	$p < 0.001$
COIN	72.1%	57.5%–81.0%	−1.3%	−5.7%–4.3%	$p = 0.020$
Delivery time	376.8 s	226.5 s–502.4 s	5.6 s	−18.9 s–22.2 s	$p = 0.011$

total, and conformality based on the tolerances of the OARs. COIN values are reported between 0% and 100%, where higher values correspond to more conformal plans.

For the autoplans we assessed the computation times. Reported times included the computation of the dose kernels for the dwell positions and the optimisation of the dwell times. The optimisations were performed on an Intel Core i7-7700 with 4 cores running at 3.6 GHz.

3. Results

All 25 autoplans had sufficient target coverage, whereas in 2/25 clinical plans the PTV coverage was slightly lower than prescribed (94.7% and 94.4%) to keep the urethral dose within the set constraint. For each case, the autoplan showed a lower urethra $D_{1\%}$ than the clinical plan with an average reduction of 6.3%-point. For the rectum and bladder D_{1cc}, the autoplans showed on average higher doses than the clinical plans: 1.2%-point for the rectum and 5.4%-point for the bladder, although all were within the clinical hard constraints as listed in table 1. On average, autoplans were more conformal than the clinical plans with an average improvement in COIN of 2.1%-point. Autoplanning also resulted in a reduced delivery time 5.6 s. Except for the rectum, the differences were statistically significant ($p < 0.05$, paired two-sided Wilcoxon signed rank test). Detailed plan parameters are presented in table 4 and figure 2.

Total computation times for autoplanning were on average 4.6 s (range 1.3–11.4). This included computation of the dose kernels (0.4 s, range 0.1–1.0). Manual planning times were not recorded for this study, but they were estimated to be <5 min.

4. Discussion

For a group of 25 low- and intermediate-risk prostate cancer patients, HDR-BT treatment plans were generated with autoplanning and compared with the clinical plans. All autoplans showed adequate target coverage and a reduced near-maximum urethra dose, the two most important criteria. The doses to the bladder and rectum of the autoplans were on average higher, but all were within the clinical constraints. The autoplans also showed on average improved conformality.

This paper investigated the feasibility and potential of using automated multi-criteria treatment planning in HDR-BT. Introducing the applied workflow as depicted in figure 1 in clinical practice has several challenges: it would require a non-certified use of the clinical TPS which would then also increase the planning time with about 5 min. Alternatively, manually entering the optimised dwell times is supported by our TPS, but time-consuming (15–20 min per patient) and error prone. We are currently exploring various options for clinical use, including formal integration of the system with the clinical TPS.

With an average of 4.6 s of total planning time, autoplanning turned out to be very fast. For most patients in this study, manual planning took less than 5 min by experienced planners. Maree *et al* (2018) investigated manual planning times for a more challenging prostate HDR-BT protocol and found a median planning time of 33 min (range 9–48). Despite such planning times, most plans could still be improved.

One option to even further reduce planning time would be to only focus on near-maximum dose reduction of the urethra, i.e. assuming that 95% coverage is always achievable. The constrained optimisation ensures compliance with the constraints in the clinical protocol (table 1). Another option is to use advanced modelling of the prioritised multi-criteria problem by using the lexicographic reference point method (LRPM), as described in Van Haveren *et al* 2017a, 2017b. Short planning times also enable to further improve multi-fraction HDR-BT: in literature there is evidence for implant displacement (Kolkman-Deurloo *et al* 2011, Aluwini *et al* 2016), so instead of performing only pre-treatment verification (Tanderup *et al* 2018), a full replanning is possible.

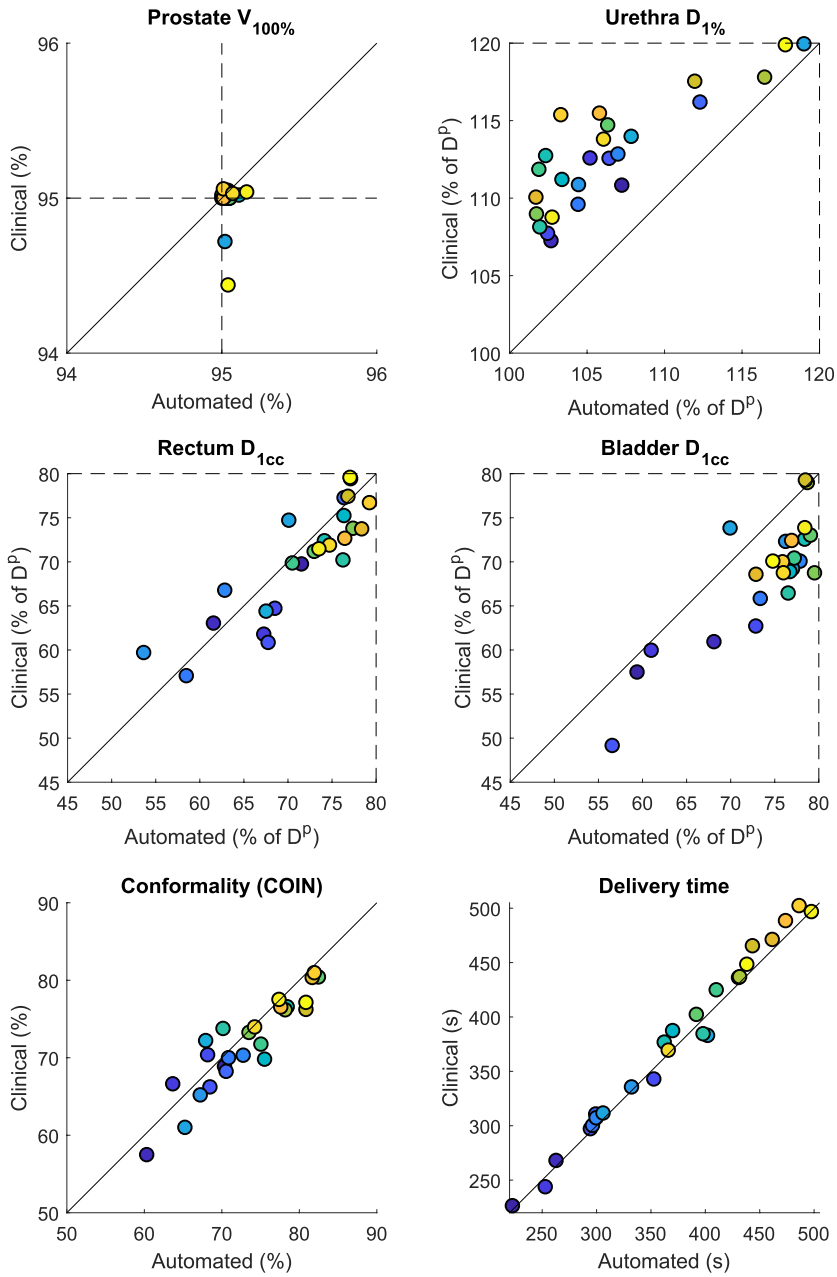

Figure 2. For the 25 study patients, comparisons of plan parameters for automatically generated plans (horizontal) and the clinical plans (vertical). Constraint levels are indicated by the dashed lines. For the OARs, markers/patients above the unity line point at lower doses for the autoplan. For the conformality index (COIN), points below the unity line show higher conformality for the autoplan. For the delivery times, markers above the unity line point at lower delivery times for the autoplans.

In this paper, we have presented an autoplanning approach that generates a single clinically relevant solution within a few seconds, by directly including the dose-volume metrics as analytic function (equation (2)) in the optimisation problem. Another analytic approach to directly include dose-volume parameters is by formulating plan optimisation as a mixed integer programming problem (Gorissen *et al* 2013). Solving such problems exactly is NP-hard (non-deterministic polynomial-time hardness) due to the branch-and-bound characteristic of the solver, and not feasible within reasonable time. Also, the performance is highly dependent on the number of dose optimisation points. Deist and Gorissen (2016) compared several approaches. Despite the small number of dose optimisation points (2750, compared to 30 765 in this paper, see table 3), runtimes were in the order of minutes, and convergence asymptotic in time. Another analysis was done by Morén *et al* (2019), who compared a dose-volume only model against one which also included a convex mean-tail-dose substitute to prevent coldspots in the tumour. While the mean-tail-dose model converged within 3 min for most cases, some other cases required 15 min to 2 h to converge.

Instead of generating a single clinically relevant plan for each patient, as performed in this study, an alternative approach is to present a range of alternative solutions, allowing the user to manually select the desired trade-off for the current patient. Cui *et al* 2018a, 2018b used a regression model to determine weights for a simulated

annealing implementation (Lessard and Pouliot 2001), and computed 14 plans to span an approximation[3] of the Pareto-front. Bouter *et al* (2019) employed a multi-criteria evolutionary solver directly on the dose-volume metrics to simultaneously generate a range of plans that approximate the Pareto-front. While the computation times were reasonable for both approaches (<30 s) and they also allow automated selection of a single plan, it is always required to compute the full range of solutions. This limits the approaches in online or real-time applications. In contrast, the implementation used in this paper can also be used to generate an approximate Pareto-front.

The question which planning method provides the best balance between plan quality and planning time remains. While the autoplans presented in this paper were consistently favourable compared to the manually generated plans, this is not a proof for global optimality from a mathematical perspective. To stimulate and enable fair comparisons, we have released the 25 cases used in this paper as part of the radiotherapy optimisation test set (TROTS) open dataset (TROTS 2016, Breedveld and Heijmen 2017). The general aims of TROTS are to enable objective comparison of different treatment planning approaches in radiotherapy, and make such data available to groups without access to medical data to encourage development of more effective and efficient planning approaches. This dataset also includes the solution which was exported to the TPS as the autoplan. However due to differences in volume definition and evaluation point selection, evaluated plan parameters differ from those reported in table 4, which were obtained by evaluation in the clinical TPS.

5. Conclusion

We developed fully automated multi-criteria treatment planning for prostate HDR-BT, and compared resulting plans with manually generated, clinically delivered plans. Compared to manual planning, the automatically generated plans:

- all had adequate target coverage, whereas 2/25 clinical plans had not
- all had consistent reduction in near-maximum urethra dose
- showed somewhat higher doses to rectum and bladder, but well within clinical constraints
- showed on average improved conformality
- had on average reduced delivery times
- had short optimisation times of 4.6 s on average.

In addition, automated treatment planning resulted in consistent, planner-independent dose distributions.

Disclosure

The Erasmus MC Cancer Institute has research collaborations with Elekta AB, Stockholm, Sweden, and Accuray Inc, Sunnyvale, USA. The Delft University of Technology—Radiation Science & Technology has research collaborations with Varian Medical Systems, Palo Alto, USA.

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