Stepping source prostate brachytherapy: From target definition to dose delivery
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Chapter 6
A comparison of inverse optimization algorithms for HDR/PDR prostate brachytherapy treatment planning

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6.1 Abstract

Background: Graphical optimization (GrO) is a common method for high-dose rate/pulsed-dose rate (PDR) prostate brachytherapy treatment planning. New methods performing inverse optimization of the dose distribution have been developed over the past years. The purpose is to compare GrO and two established inverse methods, inverse planning simulated annealing (IPSA) and hybrid inverse treatment planning and optimization (HIPO), and one new method, enhanced geometric optimization–interactive inverse planning (EGO–IIP), in terms of speed and dose–volume histogram (DVH) parameters.

Methods: For 26 prostate cancer patients treated with a PDR brachytherapy boost, an experienced treatment planner optimized the dose distributions using four different methods: GrO, IPSA, HIPO, and EGO–IIP. Relevant DVH parameters (prostate- $V_{100\%}$, $D_{90\%}$, $V_{150\%}$; urethra- D0.1cm$^3$ and D1.0cm$^3$; rectum- D0.1cm$^3$ and D2.0cm$^3$; bladder-D2.0cm$^3$) were evaluated and their compliance to the constraints. Treatment planning time was also recorded.

Results: All inverse methods resulted in shorter planning time (mean, 4–6.7 min), as compared with GrO (mean, 7.6 min). In terms of DVH parameters, none of the inverse methods outperformed the others. However, all inverse methods improved on compliance to the planning constraints as compared with GrO. On average, EGO–IIP and GrO resulted in highest $D_{90\%}$, and the IPSA plans resulted in lowest bladder D2.0cm$^3$ and urethra D1.0cm$^3$.

Conclusions: Inverse planning methods decrease planning time as compared with GrO for PDR/high-dose rate prostate brachytherapy. DVH parameters are comparable for all methods.

Keywords: Prostate neoplasms, Brachytherapy, Inverse planning, IPSA, HIPO, EGO–IIP
6.2 Background

High-dose rate and pulsed-dose rate (PDR) prostate brachytherapy are widely applied modalities in the treatment of prostate cancer [1-3]. Dose optimization is either performed intraoperatively or postoperatively, based on the target contoured on transrectal ultrasound, CT, or MRI. Graphical optimization (GrO) is a commonly used method for dose optimization at institutes performing stepping source prostate brachytherapy. With GrO, the treatment planner applies multiple drag-and-drop actions to the isodose lines [4]. This procedure requires an experienced user and is time consuming, taking up to 1 or 2 h [4-5]. Several inverse planning methods have been developed to speed up this process and improve the dose distribution. They optimize the plan by searching for the lowest value of a cost function based on a predefined set of dose objectives. Current commercially available inverse methods are inverse planning simulated annealing (IPSA) [6,7] and hybrid inverse treatment planning and optimization (HIPO) [8-10]. Both methods perform the optimization through minimization of an aggregated penalty function, meaning that all dose objectives are combined into one weighted function. The user defines a range of acceptable doses for each organ. Dose outside this range is given a linear penalty; the further outside this range, the larger the penalty. The weighted penalty function is then minimized by the simulated annealing (IPSA) [11] or the limited memory Broyden–Fletcher–Goldfarb–Shanno algorithm (HIPO) [12].

An optimized set of parameters with dose constraints and penalty weights forming the objective function, generating the desired result, is commonly called a class solution and can be used as a starting point for every patient [7]. Optimization with IPSA and HIPO starts with a general class solution, after which the objectives can be adapted for each patient to create a plan tailored to the specific implant and anatomy. Several class solutions for IPSA have been published [7,13,14]. IPSA showed superior dose–volume histogram (DVH) parameters compared with at that time conventional methods like geometric optimization (GO) and dose point optimization, which did not incorporate any anatomical information [15-17]. Positive experiences with IPSA [18] and clinical results [19] were published. Alterovitz et al. [7] showed that solutions generated by the current version of IPSA were clinically equivalent to the mathematically optimal solutions obtained using linear programming. The number of publications on HIPO were less numerous. Karabis et al. [20] demonstrated the similarity of DVH parameters of the planning target volume (PTV) between HIPO and the linear programming equivalent. Pokharel et al. [21] evaluated HIPO for real-time intraoperative planning, and in that context it included evaluation of optimization of catheter positions.

IPSA and HIPO are called a priori methods because the set of dose objectives that will lead to the most clinically suitable plan is unknown beforehand. The downside of such a method is that optimization becomes a trial-and-error process to find the optimal combination of weights and dose objectives because the effect of changing one parameter
in the objective function on all other objectives is unknown. The correlation between DVH parameters that are used to evaluate a plan and the objective function is not always evident [22,23].

Other optimization methods have been developed as well. Siauw et al. [24] and Gorissen et al. (23) formulated the problem as a mixed integer program. However, these algorithms lead to either infeasible solutions or unacceptably long computation time [22-24]. Siauw et al. therefore implemented a heuristic method for computing feasible solutions. Gorissen et al. [23] suggested to stop the solver as soon as the value of $V_{100\%}$ is satisfactory. They reported that the solution time was reduced by changing the solver parameters. Holm et al. [22] therefore proposed a model in which dosimetric indices are substituted by the so-called conditional values-at-risk. They chose to constrain dosimetric indices while optimizing dose homogeneity. Because their constraints have to be satisfied, that is, they are hard constraints, the user has to first find the set of compatible constraints that results in a feasible solution.

Another method was developed recently [25,26] as an alternative to GrO to decrease planning time and increase ease of planning. It contains a direct relation between the dose specified for an organ at risk (OAR) and the resulting dose distribution with the corresponding DVH parameters and therefore offers a straightforward alternative to IPSA and HIPO. This approach combines two new methods, enhanced geometric optimization (EGO) and interactive inverse planning (IIP). EGO is based on traditional GO [27,28], creating a homogeneous starting point. It flattens the dose distribution over the volume containing the activated dwell positions, much stronger than the traditional GO. To subsequently shape this dose distribution according to the patient’s specific anatomy, IIP was developed. Alternative to GrO, IIP is an inverse planning tool to locally adapt the dose distribution around the target and OARs.

In this article, we evaluate the dwell time optimization of existing catheter sets of 26 patients by four different methods: (1) GrO, (2) IPSA, (3) HIPO, and (4) EGO–IIP. These methods were compared to identify the method of choice for dose optimization in the clinic.

### 6.3 Methods

**Patients and treatment**

Twenty-six consecutive patients treated with PDR brachytherapy for intermediate- or high-risk prostate cancer were selected for this study. Patients selected for PDR brachytherapy have adverse prognostic factors, such as an initial prostate-specific antigen >10 ng/mL, Gleason score ≥7, or T2c–T3a. Prostate volume defined on ultrasound should be <55 cm$^3$. The PDR treatment consisted of 24 pulses with a prescribed dose of
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1.2 Gy/pulse, delivered a week after external beam radiotherapy of $23 \times 2$ Gy. All patients underwent image-guided implantation using transrectal ultrasound.

Implantation was performed in the operating room under general anesthesia. A median number of 14 MR-compatible flexible catheters were placed (range, 12–17), according to a preplan [29]. After implantation, a pelvic T2-weighted turbo spin echo MRI data set with 3-mm slice thickness was obtained for definitive treatment planning. These images were loaded into the Oncentra Brachy TPS (Elekta Brachytherapy, Stockholm, Sweden) and used for contouring of the organs and reconstruction of the catheters. Visibility of the urethra was enhanced by a transurethral catheter with a bladder balloon, placed in the operating room. The average volume of the delineated prostates was 34 cm$^3$ (range, 17.5–60 cm$^3$). The PTV equals the delineated prostate volume.

Treatment planning

For this study, a single experienced treatment planner created new treatment plans in random order for each patient for each of the four optimization methods: GrO, IPSA, HIPO, and EGO–IIP. To record the time needed for planning of GrO, we chose not to use the plans by which the patients had been treated. Furthermore, the clinical situation in which the physician may have compromised target dose for specific patients is difficult to reproduce. For all methods, the dwell positions were activated inside the target volume plus a margin of 5 mm. Creating the treatment plans with GrO started with the activation of dwell positions and a normalization of the prescribed dose on target contour points. No other method was applied to create a starting point.

Both for IPSA and HIPO, a class solution was developed and used as a starting point for optimization (Table 1). After running the optimization with the class solution, the weights of the dose objectives were modified for patient-specific optimization where necessary. Concerns have been raised about high peaks in the dwell times and large differences in neighboring dwell times when using linear penalties for inverse optimization [30-32]. We therefore used the modulation restriction parameters available in the latest versions of IPSA and HIPO. The dwell time deviation constraint (DTDC) in IPSA was set to 0.3, which was the largest value possible without compromising in plan quality. The dwell time gradient (DTG) restriction in HIPO was set to 0.2, which was also based on our own experience and corresponded well with the value used in the literature [32].

The weights that were used to obtain the final plans of IPSA and HIPO were retrospectively recorded for all patients to analyze whether our starting class solutions of IPSA and HIPO could be further improved. By calculating the median and range of the weighting parameters, we can evaluate the correctness of the class solution for these patients. If there is limited variation in the applied weighting values, there is potential to improve the class solution and further decrease planning time.
The fourth set of treatment plans was obtained with the combined use of EGO and IIP. Optimization started with applying Auto-EGO on all activated dwell positions (see Appendix 1 for more information) [25,26]. The dose was subsequently shaped according to the patients’ anatomy by increasing the minimum dose to the target and decreasing the maximum doses to the OARs. This was done by interactively entering dose limits into the software. A dose limit can be the maximum dose allowed to an organ surface or the minimum dose on the target surface. A section of the PTV and surrounding OARs can be selected, allowing for local adjustments. No class solution or fixed protocol was used.

No fine-tuning of the dose distribution using GrO was allowed after any of the planning methods.

**Planning objectives**

We aimed to create clinically acceptable plans. The dose distribution was therefore optimized according to the clinical dose objectives (Table 2). Target coverage was the main objective during treatment planning. $D_{90\%}$ was only increased when the constraints on the OARs allowed for it. The requirement for $D_{90\%}>110\%$ is often achievable with our implant geometry, which is higher than the more common constraint of $>100\%$ [2]. The constraints for rectum and bladder are similar to the Groupe Européen de Curiethérapie and European Society for Radiotherapy & Oncology (GEC-ESTRO) gynaecological recommendations [33], which advise a maximum equivalent dose in 2 Gy fractions ($\text{EQD}_2$)

<table>
<thead>
<tr>
<th>Optimization method</th>
<th>Organ</th>
<th>Minimum dose (%)</th>
<th>Weight</th>
<th>Maximum dose (%)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSA</td>
<td>PTV (surface)</td>
<td>100</td>
<td>100</td>
<td>150</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>PTV (volume)</td>
<td>100</td>
<td>100</td>
<td>150</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Urethra (surface)</td>
<td>100</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectum (surface)</td>
<td>67</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bladder (surface)</td>
<td>50</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIPO</td>
<td>PTV</td>
<td>100</td>
<td>100</td>
<td>200</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Urethra</td>
<td>125</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>83</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td>94</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal tissue</td>
<td>120</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IPSA = inverse planning simulated annealing; HIPO = hybrid inverse treatment planning and optimization; PTV = planning target volume.

The class solutions consist of the user-defined minimum and maximum doses (in percentage of prescribed dose) and accompanying weights for each organ. In the IPSA class solution, a distinction is made between surface and volume dose points. In the HIPO class solution, a normal tissue objective has to be set.
of 70 Gy for the rectum and a maximum EQD$_2$ of 90 Gy for the bladder. These equivalent doses are calculated using an $\alpha/\beta$ ratio of 3 Gy and a half time for repair of 1.5 h. Compared with the dosimetric specifications of the Radiation Therapy Oncology Group 0321 [34], our institute allows higher doses to the bladder but is more strict on urethral dose.

Plan analysis
The time needed for optimization was recorded for each plan. Plan evaluation was done with our in-house developed software that also contains the EGO–IIP planning tools. The dose was calculated in 300,000 randomly placed points, inside a box around the implant (10 mm around the activated dwell positions). Using these points, DVHs could be calculated, from which the relevant DVH parameters were extracted for all plans. For each method, the number of patients for which each constraint was achieved was also evaluated.

To evaluate the differences in dwell time distributions between the planning methods, we recorded the number of active dwell positions, along with the mean and maximum dwell times. The source strength was fixed, making it possible to compare absolute dwell times. To analyze the difference in neighboring dwell weights, we calculated the mean DTG (in seconds), that is the mean of the absolute difference in dwell time between subsequent dwell positions within all catheters. This measure can easily distinguish between plans with a large variation in dwell times and plans with more homogeneously distributed dwell times. We also recorded the total dwell time, which is in direct proportion to the total energy deposited.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Dosimetric parameter</th>
<th>Constraint (%)</th>
<th>GrO</th>
<th>IPSA</th>
<th>HIPO</th>
<th>EGO–IIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV</td>
<td>$V_{100%}$</td>
<td>&gt;95</td>
<td>19</td>
<td>17</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>$V_{150%}$</td>
<td>&lt;50</td>
<td>23</td>
<td>26</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>$V_{200%}$</td>
<td>&lt;20</td>
<td>24</td>
<td>26</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>$D_{90%}$</td>
<td>&gt;110</td>
<td>14</td>
<td>12</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>$D_{0.1cm^3}$</td>
<td>&lt;130</td>
<td>6</td>
<td>12</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>$D_{1.0cm^3}$</td>
<td>&lt;120</td>
<td>18</td>
<td>23</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Urethra</td>
<td>$D_{0.1cm^3}$</td>
<td>&lt;110</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>$D_{2.0cm^3}$</td>
<td>&lt;81</td>
<td>25</td>
<td>25</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Rectum</td>
<td>$D_{2.0cm^3}$</td>
<td>&lt;121</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>

ROI = Region of Interest; DVH = dose–volume histogram; GrO = graphical optimization; IPSA = inverse planning simulated annealing; HIPO = hybrid inverse treatment planning and optimization; EGO–IIP = enhanced geometric optimization–interactive inverse planning; PTV = planning target volume.
Statistical analysis
To test if the evaluation parameters were statistically different between the different paired groups, a Friedman test was performed, which is the nonparametric alternative to the one-way analysis of variance with repeated measures. If the hypothesis of equal groups was rejected (p < 0.05), post hoc analysis was performed to compare differences between groups using a nonparametric exact Wilcoxon signed rank test. For this test, a level of significance $\alpha = 0.02$ was used, instead of the usual value of 0.05, to limit the number of Type I errors.

6.4 Results

The resulting DVH parameters of the target (Figure 1) and OARs (Figure 2) for the different methods are displayed. Only minor differences in $V_{100\%}$ were found. However, with GrO and EGO–IIP, a higher prostate $D_{90\%}$ was obtained than with IPSA and HIPO. This higher $D_{90\%}$ was statistically significant only for EGO–IIP. As a consequence, the $V_{150\%}$ was also higher for GrO and EGO–IIP (p < 0.02). No differences in $V_{200\%}$ were found. Despite the lower $D_{90\%}$, IPSA showed a small increase in $V_{300\%}$ as compared with the other methods (p < 0.02).

A higher dose inside the prostate also resulted in a higher urethral dose for GrO and EGO–IIP (Figure 2). The urethra D1.0cm³ for GrO and EGO–IIP was significantly higher than HIPO (p < 0.02). EGO–IIP showed the largest spread in urethra D0.1 cm³. The values for the rectum and bladder were very similar, but the IPSA plans resulted in lowest bladder dose (p < 0.02). The complete (mean) DVHs for all methods are shown in Appendix 2.

With respect to compliance to the constraints (Table 2), all inverse methods appeared to perform better than GrO. IPSA resulted in improved compliance for the urethral constraints and equal compliance for all target parameters except $V_{150\%}$, which was improved to 100% compliance. HIPO improved on all the constraints, except the constraint for $D_{90\%}$, which was achieved less often than with GrO. On the other hand, HIPO showed best compliance to the urethral dose constraints of all methods. EGO also improved on all constraints except the rectal dose constraints, which were met as often as with GrO. EGO–IIP had the largest compliance to $D_{90\%}$ which led to a compromise on meeting the constraint for urethra D0.1cm³. Although not visible from the compliance to the constraints, for all methods, a clear trade-off was observed between a high target dose ($D_{90\%}$) and dose to the urethra. The differences were small for the rectum. The bladder constraint was always achieved.

Mean planning times were shortest with HIPO (4.0 ±1.5 min) and IPSA (4.3 ±1.3 min). This difference between HIPO and IPSA was not statistically significant. Planning with EGO–IIP or GrO took a few minutes longer: 6.7 ±2.8 min and 7.6 ±2.5 min, respectively.
From analyzing the weights used to create the final plans of IPSA and HIPO, the starting class solutions for HIPO and IPSA can be adapted by taking the median value for each parameter that was used in the optimization. For IPSA, the median weight on the minimal PTV dose on the surface was 180 (range, 100–200) and 150 (range, 10–200) for the volume. The weight for maximum dose to PTV was never adapted and neither was the maximum bladder dose. For the rectum, the weight was only changed for 6 patients. The median weight on the maximum urethral dose was 15 (range, 5–50) vs. 10 in the class solution. With HIPO, the weight on the minimum PTV dose was never adapted with respect to the starting class solution. The weights for the maximum PTV dose and maximum urethral dose were regularly adapted, ranging from 1 to 20 (PTV) and 2–17 (urethra). Bladder, rectum, and normal tissue weights were only changed in two, three, and four cases, respectively.

Figure 1: The DVH parameters for the target: (a) $V_{100\%}$, $V_{150\%}$, and $V_{200\%}$ and (b) $D_{90\%}$. The box plots extend over the IQR. The whiskers extend over the entire range (without the outliers, which are defined as points further than $1.5 \times$ IQR from the median). The dots represent individual patient points, and line segments between bars indicate a statistically significant difference. An asterisk (*) indicates that the corresponding p-value lies between 0.01 and 0.02; otherwise, $p < 0.01$. GrO = graphical optimization; IPSA = inverse planning simulated annealing; HIPO = hybrid inverse treatment planning and optimization; EGO–IIP = enhanced geometric optimization–interactive inverse planning; DVH = dose–volume histogram; PD = prescribed dose; IQR = interquartile range.
Dwell time distribution
The number of dwell positions with a nonzero dwell time was largest with HIPO (Table 3). Mean and maximum dwell times and DTG were therefore lowest with HIPO ($p < 0.02$). With IPSA, the lowest number of dwell positions was used, which led to larger dwell times and a larger DTG. Even when correcting for differences in total dwell time between the methods, the mean dwell time and DTG were highest for IPSA ($p < 0.02$). Large maximum dwell times were also observed for EGO–IIP.

6.5 Discussion
Dwell time optimization using an inverse method decreased planning time as compared with GrO but did not lead to overall significantly better treatment plans. However, com-
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Compliance to the constraints was improved using the inverse methods. The different methods resulted in some differences in DVH parameters. EGO–IIP gave the smallest benefit in planning time and resulted in DVH parameters most similar to GrO. The main difference between IPSA and the other methods was the number of dwell positions used, which was smallest for IPSA.

This is the first study comparing a comprehensive set of planning methods. IPSA and HIPO are the main available methods for a large group of users. To avoid the trial-and-error procedure that is associated with IPSA and HIPO and/or to maintain the local control over the dose distribution, some institutes prefer GrO. EGO–IIP was developed as an option for these users to improve the ease in planning and reduce the time needed to realize a plan meeting the clinical objectives. EGO–IIP is therefore added to this set as an alternative to GrO. This study did not compare all existing methods. Recently developed methods like Inverse Planning by Integer Program (IPIP) [24], the method presented by Holm et al. [22] and that of Gorissen et al. [23], were not included. This choice was based on availability of and experience with the current restricted set of methods. Furthermore, dwell weights of existing implants were optimized in this study, and no catheter position optimization methods were compared.

IIP was developed as a computerized form of GrO. The main advantages of the combined use of EGO–IIP are that the user immediately obtains the dose limit he or she enters into the software, and local adaptation of the dose distribution is possible. Being able to

### Table 3. Dwell time analysis of all patients (mean ± 1 standard deviation)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GrO</th>
<th>IPSA</th>
<th>HIPO</th>
<th>EGO–IIP</th>
<th>Post hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active dwell positions</td>
<td>154 ± 35</td>
<td>105 ± 36</td>
<td>168 ± 41</td>
<td>145 ± 40</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>Mean dwell time (s)</td>
<td>1.3 ± 0.3</td>
<td>2.0 ± 0.7</td>
<td>1.2 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>Maximum dwell time (s)</td>
<td>9.5 ± 3.3</td>
<td>9.2 ± 3.8</td>
<td>6.6 ± 3.2</td>
<td>13.5 ± 7.0</td>
<td>2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>Total dwell time (s)</td>
<td>194.7 ± 41.7</td>
<td>189.5 ± 39.6</td>
<td>189.3 ± 38.6</td>
<td>196.7 ± 42.4</td>
<td>1, 2, 5, 6</td>
</tr>
<tr>
<td>DTG</td>
<td>0.5 ± 0.1</td>
<td>0.9 ± 0.3</td>
<td>0.3 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>2, 3, 4, 5, 6</td>
</tr>
</tbody>
</table>

GrO = graphical optimization; IPSA = inverse planning simulated annealing; HIPO = hybrid inverse treatment planning and optimization; EGO–IIP = enhanced geometric optimization–interactive inverse planning; DTG = dwell time gradient.

GrO–IPSA (1); GrO–HIPO (2); GrO–EGO–IIP (3); IPSA–HIPO (4); IPSA–EGO–IIP (5); HIPO–EGO–IIP (6).

The column post hoc analysis indicates the pair for which the difference is statistically significant (p < 0.02).
interactively enter dose limits as used in the clinic makes EGO–IIP an intuitive package. This study showed that compared with GrO the planning time is only slightly reduced by EGO–IIP and that DVH parameters were comparable. The overall appearance of the GrO and EGO–IIP plans in terms of isodose pattern was very similar. With EGO–IIP, all dose constraints were met equally (rectum and bladder) or more often (PTV and urethra) than with GrO, proving that EGO–IIP is a suitable and valid alternative for GrO users. Because of the ease of real-time interaction, it does not depend on the development of a class solution. Ruotsalainen et al. [35] also emphasized the benefits of interactive optimization. They performed interactive multiobjective optimization of brachytherapy cervix treatments with dosimetric indices as input. On the other hand, planning time might be reduced by the implementation of a class solution, which is currently under development.

No quality indices are presented in this study because the differences in conformity and other quality indices were marginal. The conformation number (36) was slightly better with IPSA (0.65 ± 0.05) and HIPO (0.64 ± 0.06) than with GrO (0.60 ± 0.06) and EGO–IIP (0.59 ± 0.05). With these latter methods, more dwell positions at the cranial and caudal sides of the prostate are used, which probably caused a small but statistically significant difference. These conformity values were comparable or lower than those found in other publications [4,37], which could be a consequence of a high $D_{90\%}$ in our study or the smaller number of implanted catheters [38]. The relatively low conformity could also be related to the peripheral geometry of our implanted catheters.

We aimed to create clinically suitable plans, allowing us to compare the different methods in the clinical setting, instead of applying just one fixed class solution for all patients. That would not give results usable in the clinic and would not allow the comparison of planning times. Our approach does result in some degree of subjectivity in the planning process. For instance, the treatment planner may choose to increase prostate $V_{100\%}$ and $D_{90\%}$ at the cost of a higher urethral dose and vice versa. For another treatment plan, a lower rectal dose may be preferred. Part of the planning process is a matter of preference and/or choice. This was confirmed by our results that irrespective of planning method, the main trade-off is that between a higher $D_{90\%}$ (and $V_{150\%}$) and higher dose to the urethra. It should be noted that performing this study with other planning objectives, the results may be different. However, the current results suggest that these four methods are equally capable of achieving the objectives, provided that good class solutions are available. We also did not study the performance of these methods on patient-specific adjustments of existing plans, which would give different results, also in terms of planning times. IPSA and HIPO may be less suited for this purpose; in clinical practice, fine-tuning an existing plan is usually accomplished with GrO [5,21] and [23]. IIP may be a suitable alternative for this.

Although GrO is the clinical standard at our department, we did not use the clinical
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plans. All patients were graphically reoptimized for this study to enable an unbiased comparison in terms of planning time and DVH parameters. Treatment planning using GrO was faster than the 1–2 h reported by earlier articles [4,5]. In clinical practice, the plan can still be adapted according to the physician’s wishes after the treatment planner has finished. In this study, such possible patient-specific preferences of the physician were eliminated. Nevertheless, the plans created in this study were of high clinical standard and presented the best possible trade-off the treatment planner could find. Because of the long experience in GrO, the time needed to create a plan was 14 min at most, which may be different at other institutes. It must be noted that IPSA and HIPO were extensively tested to acquire the class solutions. Therefore, although planning times might be different at other institutes, we feel that the comparison was not biased by limited experience with one of the methods.

Although all methods resulted in high-quality dose distributions, the distributions of the dwell weights were different. It was found that the IPSA plans used the smallest number of nonzero dwell weights, despite the use of the DTDC, which obviously resulted in higher mean dwell times and larger variation (described by the DTG). No clinical evidence has been reported of the importance of homogeneity of dwell times, but large dwell times could lead to hot spots of volumes receiving a high dose around these specific dwell positions [32,39]. These volumes are generally avoided if possible [32,40]. This is supported by the American Brachytherapy Society and the Radiation Therapy Oncology Group 0321 study, stating that a minimum number of 14 catheters is required to avoid unnecessary hot spots [34,41]. A DTDC of 0.3 was applied for IPSA and a DTG restriction of 0.2 for HIPO. The choice for these numbers was based on experience. A larger value for the DTDC may generate smoother dwell times, but imposing larger restrictions leads to clinically unacceptable solutions [32,42]. The larger DTGs did not result in large volumes of the prostate receiving at least 150% of the dose. The $V_{150\%}$ of IPSA and HIPO was significantly lower than of GrO and EGO–IIP. For the volumes receiving a very high dose, it was the other way around: $V_{300\%}$ of IPSA was larger than the $V_{300\%}$ of the other three methods. The clinical relevance of volumes with such high doses is still unknown. In the study by Baltas et al. [32], the use of a modulation restriction in HIPO slightly increased the $V_{150\%}$, whereas decreasing the $D_{90\%}$ and $V_{100\%}$ as compared with their unrestricted plans. This was not observed in our study, where the lower $V_{150\%}$ for IPSA and HIPO can probably be explained by the lower $D_{90\%}$ of these methods.

The use of less dwell positions can partly be explained by the selection of catheters that are used to create a dose distribution. With IPSA, in 35% of the cases, one or two catheters were not used. For GrO, in 23% of the cases, one or two catheters were not used. With EGO–IIP, there was only one case (4%) in which a catheter was omitted during planning. With HIPO, no catheters were fully deactivated. The use of less needles might be beneficial in terms of implantation time, cost, and possibly reduce trauma-related morbidity [43]. On the other hand, using a very limited amount of catheters is associ-
ated with a high urethral dose and can lead to increased acute urinary toxicity [44]. In addition, the use of more catheters improves homogeneity and conformity of the dose distribution (38).

The class solutions used in this study were in-house developed and therefore differ from class solutions reported in the literature [7,13,14]. The choice of a class solution is usually specific to an institute, their method of implantation, and possibly even prostate volume. The class solutions of IPSA and HIPO were not the same, partly because of the differences in formulation of the dose objectives. With IPSA, separate dose objectives can be assigned to surface and volume points of a structure, whereas with HIPO, one dose range per organ is defined. To obtain sufficient dose coverage with HIPO, the maximum dose for the PTV was set to 200%, making HIPO less strict on high doses than IPSA, where the maximum PTV dose was set to 150%, albeit with a relatively lower weight. Nevertheless, it did not result in a higher $V_{150%}$ than IPSA. The analysis of the final objective functions used to create the plans showed that the initial class solutions had been chosen well. For IPSA, the initial weight on the minimum dose to the PTV could be higher and the weight on the maximum urethral dose. However, the spread of the values was too large for it to result in a decrease in planning time. For HIPO, the weight on the maximum urethral dose should be slightly higher. However, also here, no reduction in planning time can be expected.

### 6.6 Conclusions

For the 26 prostate cases from our institute, high-quality treatment plans could be obtained with all treatment planning methods (GrO, IPSA, HIPO, and EGO–IIP). All methods were comparable in terms of DVH parameters. The choice of planning method therefore remains one of user preference. The results may be different for other implant geometries and a different number of catheters implanted in the prostate.

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### 6.7 Appendix

**Appendix 1. Enhanced geometric optimization–interactive inverse planning**

In this article, the combined use of EGO and IIP was applied for treatment planning. The planning concept is straightforward: we start with EGO, creating a dose distribution as homogeneous as possible, then use IIP to shape this dose according to the patients’ anatomy.
EGO is an enhanced form of the classical GO. It increases the difference between the weight as calculated by GO and the normalized weight of 1 with a strength factor, $S_{EGO}$. A second range parameter, $R_{EGO}$, is related to the classical GO algorithm, providing a continuous transition between GO for volume and distance implants. To find the highest possible dose homogeneity in the implanted volume, an implementation of EGO was applied that uses a binary search algorithm over different values of the $S_{EGO}$ and $R_{EGO}$ parameters to find the dose distribution with the highest quality index (45). This automated step (Auto-EGO) was applied on all dwell positions within the target surface plus a given margin of 5 mm. Because EGO is not anatomy based, IIP was used after Auto-EGO to shape the dose distribution according to the existing patient’s anatomy.

In IIP, the lowest and highest doses found on the contours of all regions of interest (ROIs) are displayed in the user interface, as well as the corresponding volumes of each ROI receiving at least a given percentage of the prescription dose. The treatment planner changes the current limits for the lowest and highest doses found on the ROI contours to dose limits used clinically. After each change, the volumes for given dose values inside the ROIs are updated.

IIP lowers the highest dose found on an ROI to a preferred value as follows. It (1) searches for the highest dose on the contours of the ROI and then (2) reduces the dwell weights in the most nearby dwell position(s) with a few percent. IIP repeats (1) and (2) until the highest dose on the ROI is below or equal to the user-defined maximum dose. These steps that are executed after changing a dose limit are practically real time, and the user can immediately evaluate the new dose distribution. Planning with IIP is therefore an inverse interactive process. It is also possible to directly enter the desired volume receiving at least a certain dose ($V_{xx\%}$) or the maximum dose to a certain volume ($D_{xxcm^3}$). IIP then iterates by itself until this value is obtained, after which the user evaluates the effect on the entire dose distribution.
Figure Appendix 2: Mean DVHs for the PTV, rectum, urethra, and bladder, shown for the four different methods. The lower error bars represent the first quartile (25th percentile), and the upper error bars represent the third quartile (75th percentile). The data points on the x-axis are slightly jittered to improve visualization.
6.8 References


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