Dosimetric and Radiobiological Evaluation of Hybrid Inverse Planning and Optimization for Cervical Cancer Brachytherapy

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Abstract. *Aim: To compare manual graphical optimization (GrO) with hybrid inverse planning optimization (HIPO) of cervical cancer brachytherapy treatment plans using physical and radiobiological tools. Patients and Methods: Ten patients suffering from cervical cancer, treated with pulsed brachytherapy using GrO plans, were included in the study. For each patient, four different HIPO class solutions with different dose objectives to the target and constraints to the organs at risk (OAR) produced four optimized plans, that were each compared to the corresponding GrO plan. Class solution in HIPO is a set of parameters consisting of dose constraints and penalty weights, which are used for optimization. The comparison was based on the following dosimetric parameters: conformity index (COIN), minimum dose received by 98% and 90% of the high-risk clinical target volume (represented by D98 and D90, respectively), and the minimum dose imparted to 2 cm^3 (D_{2cm}^3) of the most exposed OAR i.e. bladder, sigmoid colon or rectum. The HIPO class solution which produced plans with overall better dosimetric parameters was selected and its plans were compared with manual GrO plans from a radiobiological viewpoint based on the calculated complication-free tumour control probability, P_+. Results: The average COIN for the GrO and the selected HIPO plans were 0.22 and 0.30, respectively. The median COIN of the GrO and the HIPO plans were not statistically different ($p>0.05$, Wilcoxon test). The relative percentage difference of the averaged P^+ values between the HIPO and GrO plans evaluated together with the external beam radiation therapy plans was 0.01%, 0.37% and 0.98% for the bladder, sigmoid colon and rectum, respectively. The lowest P_+ value for all the plans was 98.44% for sigmoid colon. Conclusion: HIPO presented comparable results in relation to manual planning with respect to dosimetric and radiobiological parameters.*

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Anatomy-based inverse planning in brachytherapy was successfully implemented into treatment-planning systems (TPS) more than a decade ago (1-4). Among its competitive advantages compared to manual graphical optimization (GrO) are reduction of subjectivity, less time required to generate a treatment plan, sparing of tissues outside the target, and increased target coverage (5-8). Certain treatment planning and optimization approaches have shown potential to address specific challenges posed by different anatomical regions (8-10). The hybrid inverse planning optimization (HIPO) algorithm developed by Karabis *et al.* (11) incorporates specific tools which allow HIPO plans to control the spatial dose distribution and avoid hot-spots (10, 12). These features enable HIPO plans to mimic the frontal plane 'pear'-shaped dose distribution of cervical cancer brachytherapy, which has produced good clinical results through standard and GrO planning (13). The differential features of brachytherapy in relation to external-beam radiation therapy (EBRT), coupled with adequate optimization offer the option of escalating the dose to the tumour while sparing organs at risk (OARs). However, within an optimization algorithm, there is a need to assess the dose objectives for the planning target volume (PTV) and OAR constraints that produce the best treatment plans according to the treatment aim (13).

The aim of the present work was to compare four HIPO class solution plans with reference to the GrO plans from a dosimetric point of view. Among the HIPO class solutions, the HIPO class type plan resulting in the highest conformity index, acceptable dose to the PTV and the lowest doses to OARs was selected and further compared to the GrO plans from a radiobiological perspective by means of the complication-free tumour control probability, P_+.

Table I. *Set of objectives – dose constraints and importance factors (weights) for hybrid inverse planning optimization (HIPO) plans for one fraction (8 Gy). The gross tumour volume (GTV) has higher priority over the high-risk clinical target volume (HR-CTV). The other regions of interest (ROIs) do not intersect and are not assigned priority.*

ROI	Usage	Min. weight	Min. (Gy)	Max. (Gy)				Max. weight	Priority
				HIPO A	HIPO B	HIPO C	HIPO D		
Bladder	OAR	-	-	6.8	7.3	6.8	7.3	10	-
Sigmoid colon	OAR	-	-	4.5	3.7	5.1	4.8	15	-
Rectum	OAR	-	-	4.5	3.7	5.1	4.8	10	-
GTV	GTV	15	12.0	24.0	24.0	24.0	24.0	0.1	1
HR-CTV	PTV	50	8.0	24.0	24.0	24.0	24.0	1	2
NT	NT	-	-	16.0	16.0	16.0	16.0	0.1	-

NT, Normal tissue; OAR, organ at risk; PTV, planning target volume.

Patients and Methods

Patients and treatment. This study was based on dose–volume histograms of 10 patients, treated for carcinoma of the cervix between the years 2012-2013 at Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden, using the Oncentra® Brachytherapy treatment planning system (version 4.1; Nucletron, Elekta AB, Stockholm, Sweden). The staging of the malignant disease according to the International Federation of Gynecology and Obstetrics (FIGO) (14-16) varied from IB2 to IIIB. The fractionation of the brachytherapy regimen was chosen according to the NOCECA protocol (17, 18), which is a Nordic protocol for cervical cancer management with radiation therapy (RT) (18) and has two mutually exclusive variants, NOCECA I and NOCECA II. In NOCECA I, the patients are treated with EBRT giving 50 Gy in 25 fractions to the target, 45 Gy in 25 fractions to the pelvis in the same plan, receive a boost of pulsed intracavitary brachytherapy of 24 Gy in three fractions and the total treatment (EBRT plus brachytherapy) is given in six weeks. Each brachytherapy fraction is divided into six pulses of 1.33 Gy and the time interval between two pulses is 1 h. NOCECA II differs from NOCECA I in that it adds an extra EBRT dose boost to the target of 10 Gy in five fractions after brachytherapy, the total brachytherapy dose is 16 Gy and the treatment is given in seven weeks. In the NOCECA protocols, the OAR tolerance doses for EBRT together with brachytherapy expressed as equivalent dose in 2 Gy fractions (EQD2) are 90 Gy_{EQD2} for the bladder and 70 Gy_{EQD2} for the rectum and sigmoid colon assuming an intrinsic sensitivity to fractionation as described by the ratio of the parameters of the LQ model for cell survival (19) of α/β=3 Gy (20, 21).

The brachytherapy was delivered with the Nucletron Ring computerized tomography-magnetic resonance (CT-MR) applicator set, together with a Smith sleeve.

Contouring. The delineation of volumes of interest was performed based on T2-weighted MR images (1.5 Tesla). The high-risk clinical target volume (HR-CTV), CTV and bladder were delineated by a physician. For the rectum and the sigmoid colon, only the part adjacent to the target was delineated as an OAR. The applicator volume was delineated by a medical physicist. The dose was prescribed to the HR- CTV (20, 21).

Treatment planning. In addition to the GrO plan that was actually delivered for each brachytherapy fraction, four class solutions HIPO A, HIPO B, HIPO C and HIPO D, with different objectives for the target and constraints for OARs, were retrospectively generated for the same fractions. The optimization parameters for the HIPO plans were derived from the NOCECA and GEC ESTRO protocols (Table I). The tolerances in the GEC ESTRO recommendations are 90 Gy_{EQD2} for the bladder and 75 Gy_{EQD2} for the rectum and sigmoid colon, (α/β=3 Gy) (20, 21).

HIPO A and HIPO B class solutions resulted from implementation of NOCECA I and NOCECA II, respectively. HIPO C and HIPO D resulted from the GEC ESTRO OAR tolerances but their prescribed physical dose to target for brachytherapy treatment was derived from NOCECA I (24 Gy) and NOCECA II (16 Gy), respectively. Thus, the maximum value for the dose per fraction that should be imposed as a constraint in the optimization of the HIPO plans was calculated by determining first the equivalent dose in (2 Gy) fractions to the OAR in EBRT, $EQD2_{EBRT}$ (α/β=3 Gy), assuming that the OARs receive the maximum dose prescribed to the target and then calculating the maximum dose that could be delivered during the brachytherapy treatment without exceeding the tolerance dose specified in the protocol, $EQD2_{BT}$ (α/β=3 Gy).

Notwithstanding differentiated target objectives and OAR constraints, the remaining parameters were kept the same for all the HIPO class solutions (Table I). The weights assigned in the planning optimization for the minimum dose to the target are higher than the weights for the maximum dose to the target since it was assumed that it is more important to avoid cold spots in the target than hot spots. In contrast to the target maximum dose weights, the weights associated with the maximum dose to OARs are relatively higher in order to prevent the irradiation of the OARs with doses above the tolerance level. The highest weight was set for the maximum dose to the sigmoid colon based on the results of a previous study in which it was observed that keeping the dose to the sigmoid colon below the tolerance level might be potentially problematic when the plan is produced using inverse optimization (13). The dwell time gradient restriction parameter recommended for HIPO optimization for prostate high-dose-rate brachytherapy is 0.2 (22, 23) and this value was adopted for all the inverse plans in this study.

Plan evaluation. Dosimetric criteria: The physical parameters evaluated were the conformity index (COIN), minimum dose to 98%

and 90% of the target volume, *D*98 and *D*90, respectively and minimum dose to the most exposed 2 cm^3 volume of an OAR, *D*2cm^3. COIN is defined as

$$COIN = \frac{V_{ref,TV}^2}{TV \cdot V_{ref}} \left\{ \prod_{i=1}^{n} \left[1 - \frac{V_{OARcrit,i}}{V_{OARi}} \right] \right\}$$

where $V_{ref,TV}$ is part of the target volume (TV) that receives the reference dose, V_{ref} is the volume which receives the reference dose (24, 25), V_{OAR} is the OAR volume and VOARcrit is the OAR volume which receives the critical dose, which is 90% and 63% of the prescribed dose for the bladder and sigmoid/rectum, respectively (12, 20, 21).

The two-sided Wilcoxon rank sum test tool was used for statistical analysis related to the comparison of the plan based on dosimetric criteria.

Radiobiological criteria: In order to assess if the differences in dose distributions corresponding to the different plans would result in differences with respect to treatment outcome, the GrO and the HIPO class solution which produced plans with the average highest COIN and the lowest D2cm^3 doses to the OAR were further compared with respect to the P_+ (26-28), which is expressed as:

$$P_+ = TCP - NTCP + \delta(1 - TCP) \cdot NTCP$$

where *TCP* is the tumor control probability, *NTCP* is the normal tissue complication probability for a specific OAR and δ is a fraction of patients assumed to have uncorrelated responses for *TCP* and *NTCP*. This study assumes δ≈0.2 (26).

TCP and *NTCP* were calculated using the generalized equivalent uniform dose (*gEUD*) (29, 30). The *gEUD* was computed after calculation of equivalent dose in 2 Gy per fraction (*EQD2*) for each bin in the dose–volume histogram (31, 32).

Assuming the linear quadratic model for cell killing and Poisson statistics, *TCP* is calculated as follows:

$$TCP = exp\left(-N_0 \times {SF_2}^{D/2}\right)$$

where N_0 is the initial number of clonogenic cells in the target, SF_2 is the surviving fraction at 2 Gy, *D* is the sum of brachytherapy and EBRT *gEUD*.

The normal tissue response was calculated using the Probit model:

$$NTCP = \frac{1}{2}\left(1 - Erf\left[\gamma_{50}\sqrt{\pi}\left(1 - \frac{D}{D_{50}}\right)\right]\right)$$

where D_{50} is the uniform brachytherapy and EBRT organ dose that gives 50% response, γ is the maximum normalized dose response gradient for the OAR in question.

The radiobiological parameters used in the calculations were the same as the ones used in our previous study (32) and were taken from literature (21, 31, 33).

Results

The HR-CTV for the 10 patients studied ranged from 11.3 to 45.1 cm^3. For each of the patients, four plans were made in addition to the GrO plan based on the four class solutions HIPO A, HIPO B, HIPO C and HIPO D. All plans were deemed clinically acceptable and were evaluated with respect to COIN, *D*98 *D*90 and *D*2cm^3.

The GrO and HIPO box-and-whisker plots for COIN are displayed in Figure 1. The highest median COIN was found for the HIPO B plan; however, the median COIN of each of the HIPO solutions was not significantly different from the median COIN by GrO ($p>0.05$).

The median *D*98 and *D*90 of the HIPO class solutions compared with the corresponding GrO plan doses result in similar values ($p>0.05$) (Figure 2). The comparison between plans with respect to the median *D*2cm^3 imparted to the most exposed region of the bladder, sigmoid colon and rectum is shown in Figure 3.

HIPO A and HIPO B class solutions produced plans resulting in significantly lower median *D*2cm^3 doses to the sigmoid colon in comparison to the GrO plans ($p<0.05$). HIPO C and HIPO D plans also gave lower median *D*2cm^3 to the sigmoid colon but were not significantly different ($p>0.05$). In contrast to GrO plans, all inverse plans gave a lower median *D*2cm^3 to the rectum but were not significantly different ($p>0.05$). For the bladder, however, the inversely optimized plans resulted in slightly higher median doses per fraction to the most exposed 2 cm^3 volume than the GrO plan, the difference, however, not being statistically significant ($p>0.05$).

Among the inverse plans, HIPO B gave better dosimetric results with regard to COIN (Figure 1), and good overall sparing of OARs (Figure 3) and was selected for the radiobiological comparison with the GrO; however, it is acknowledged here that HIPO A, HIPO C and HIPO D gave better values of *D*98 and *D*90, but their median values were not significantly different from the HIPO B plan ($p>0.05$).

The radiobiological evaluation of the plans was carried-out by calculating the overall P_+, which takes into account the *TCP* and the *NTCP*. The brachytherapy dose distribution was assumed to be given by the GrO and HIPO B plans, respectively, while the dose distribution for EBRT was considered to be the same. The average values of P_+ are presented in Table II. The very high values result from a probability of controlling the tumour of almost 100% accompanied by a very low probability of complications for the OARs.

Discussion

There have been studies showing the comparability of GrO and HIPO plans for cervical cancer brachytherapy from dosimetric and target coverage perspectives (5, 10, 12) but to the best of our knowledge, this is the first study in which a combined dosimetric and radiobiological analysis of GrO and HIPO plans is presented in this fashion. The principal objective of treatment plan optimization is to maximize P_+. One important challenge,

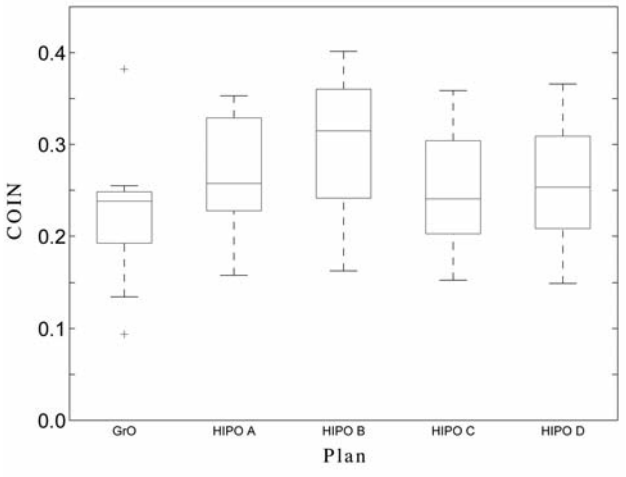

Figure 1. *Box-and-whisker plots comparison of conformity index (COIN) values for the graphical optimization (GrO) and hybrid inverse planning optimization (HIPO) class solutions. Inside each box, the horizontal line indicates the median value, the edges of the box are the 25th and 75th percentiles and the whiskers extend to the most extreme points. The plus signs represent outliers (cases that fall outside the range of the other values).*

however, when inverse planning is used for devising RT plans is to determine the suitable objectives, constraints and weights which will mirror the experience of a dose planner trained in producing good plans through manual optimization. It was, therefore, the aim of this study to explore the possibility of finding suitable parameters for the inverse planning and explore the feasibility of using class solutions instead of manual planning. Thus, four different HIPO class solutions were established and tested to guide the choice of one solution, which would be further selected for the radiobiological comparison with GrO plans by means of P_+.

With respect to the COIN, the average COIN for the 10 patients resulting from the HIPO B plans was higher (0.30) than the corresponding average resulting from the manually optimized GrO plan (0.22). All the HIPO plans resulted in higher average COIN in comparison with GrO plans. The largest average COIN corresponded to the HIPO B plans, which imposed the most severe constraints to the maximum dose to rectum and sigmoid colon and as expected, limiting the maximum dose to these two OAR to only 3.7 Gy per fraction. This corresponded to keeping the dose to the rectum and sigmoid colon below the tolerance dose of 70 Gy when brachytherapy is added to the EBRT and consequently resulted in the lowest values for the most exposed 2 cm^3 volume of the sigmoid colon and rectum in comparison not only to the manually optimized plan but also to the HIPO A, HIPO C and HIPO D class solution plans. Thus, the HIPO B plan may also present the potential to further spare the sigmoid colon and rectum while giving acceptable doses to the target.

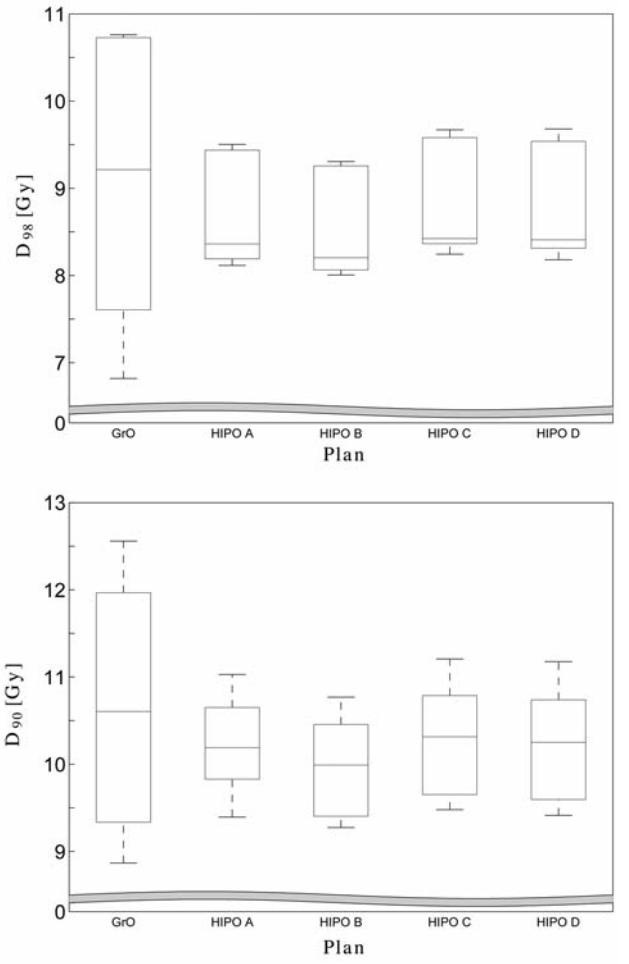

Figure 2. *Box-and-whisker plots comparison of minimum dose to 98% (D98; upper panel) and 90% (D90; lower panel) of the target volume, respectively, for the graphical optimization (GrO) and hybrid inverse planning optimization (HIPO) class solutions.*

For the radiobiological evaluation of the treatment plans, the P_+ was calculated in relation to one OAR at a time. The P_+ values for the bladder, sigmoid colon and rectum, were above 98.44% for all GrO and HIPO B brachytherapy treatment plans evaluated together with the EBRT plans. Although there are no guidelines stating the intervals of acceptability of P_+, its ideal value is 100%. The high values of P_+ found in this study are supported by clinical observations in terms of good treatment outcome (18, 34). The relative percentage difference of the averaged P_+, between GrO and HIPO plans $[(P_{+,HIPO} - P_{+,GRO})/P_{+,GRO}]$ was 0.01%, 0.37% and 0.98% for the bladder, sigmoid colon and rectum, respectively. Although small, these differences indicate that the HIPO plans were slightly superior to those by GrO and therefore automated inverse planning could lead to results at least as good as manual graphical optimization. However, it has to be acknowledged that the

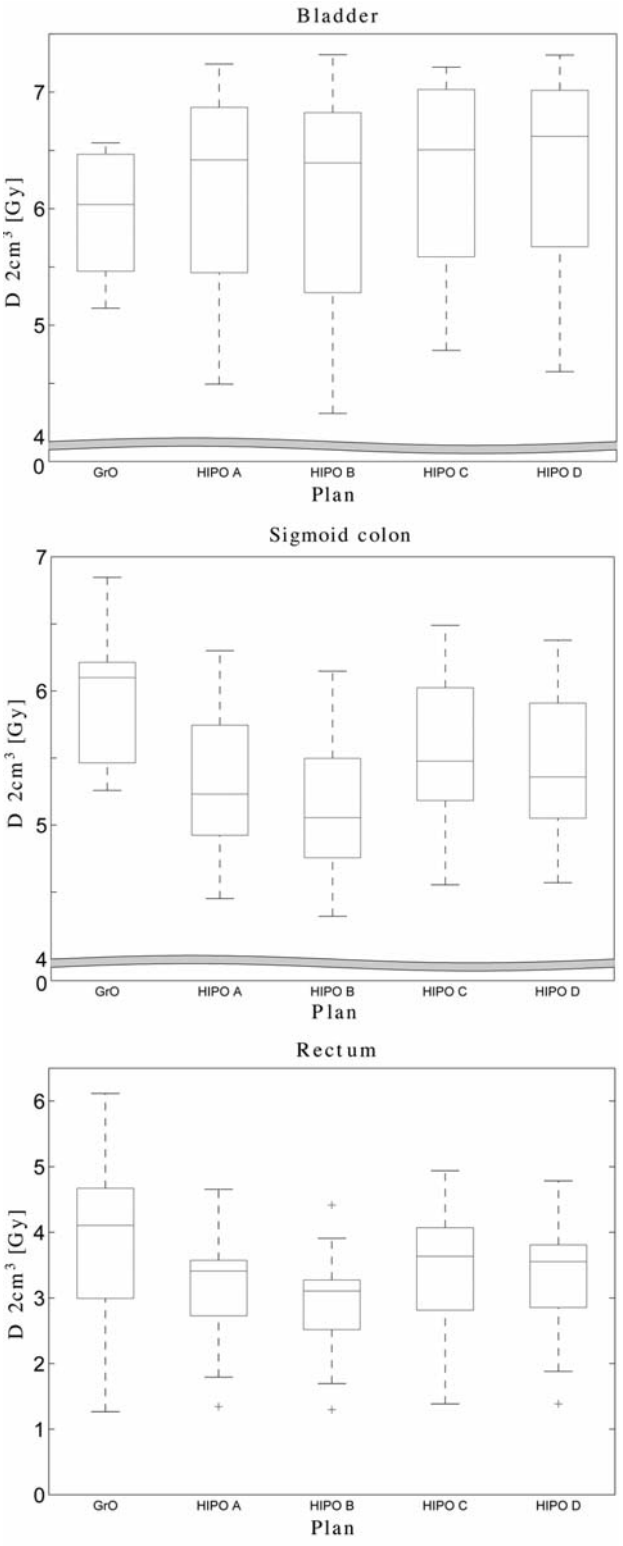

Figure 3. *Box and whisker plot comparison of median minimum dose to the most exposed 2 cm³ volume of an organ at risk (OAR), D2cm³, for the graphical optimization (GrO) and hybrid inverse planning optimization (HIPO) class solutions for bladder (upper panel), sigmoid colon (middle panel), rectum (lower panel).*

Table II. *Averaged values of complication-free tumour control probability (P+) and the corresponding relative percentage difference.*

ROI	$P_{+,\mathrm{HIPO}}(\%)$	$P_{+,\mathrm{GRO}}(\%)$	$(P_{+,\mathrm{HIPO}}-P_{+,\mathrm{GRO}})/P_{+,\mathrm{GRO}}(\%)$
Bladder	99.76	99.75	0.01
Sigmoid colon	98.80	98.44	0.37
Rectum	99.94	98.97	0.98

ROI, Region of interest; HIPO, hybrid inverse planning optimization; GrO, graphical optimization.

calculation of the P_+ heavily depends on the choice of the modelling parameters describing the sensitivity of cells to radiation and therefore a study of the robustness of the results accounting for the uncertainties in the radiobiological parameters is warranted, but is beyond the scope of this study.

Conclusion

The fine-tuned class solution of HIPO B presented in this study leads to comparable results in relation to GrO plans both for dosimetric as well as radiobiological end-points.

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Conflicts of Interest

None to declare.

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