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 cm³ (D2cm³) 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.

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, \( P_+ \).
in 2 Gy fractions (EQD2) are 90 GyEQD2 for the bladder and 75 GyEQD2 for the rectum and sigmoid colon. Thus, the physical dose to target for brachytherapy treatment was derived from the GEC ESTRO OAR tolerances but their prescribed fractionation was adopted for all the inverse plans in this study.

The tolerances in the GEC ESTRO recommendations are 90 GyEQD2 for the bladder and 75 GyEQD2 for the rectum and sigmoid colon, \((\alpha/\beta=3\text{ Gy})\) (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, \(\text{EQD2}_{\text{EBRT}}(\alpha/\beta=3\text{ Gy})\), 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, \(\text{EQD2}_{\text{RT}}(\alpha/\beta=3\text{ Gy})\).

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 OARs when the planning optimization is 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 distributions corresponding to the different plans would result in radiobiological criteria.

The analysis related to the comparison of the plan based on dosimetric for the bladder and sigmoid/rectum, respectively (12, 20, 21).

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**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 $D_{2cm^3}$ 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 $\delta$ is a fraction of patients assumed to have uncorrelated responses for $TCP$ and $NTCP$. This study assumes $\delta=0.2$ (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:

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

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:

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

where $D_{50}$ is the uniform brachytherapy and EBRT organ dose that gives 50% response, $\gamma$ 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 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,
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$^2$ 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.

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 $[(P_+\text{HIPO} - P_+\text{GrO})/P_+\text{GrO}]$ 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
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.

**References**


