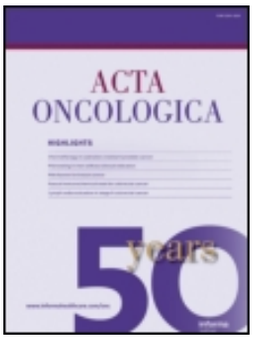

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ORIGINAL ARTICLE

Dosimetric evaluation of manually and inversely optimized treatment planning for high dose rate brachytherapy of cervical cancer

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ABSTRACT

Background. To compare five inverse treatment planning methods with the conventional manually optimized planning approach for brachytherapy of cervical cancer with respect to dosimetric parameters.

Material and methods. Eighteen cervical cancer patients treated with magnetic resonance imaging (MRI)-guided high dose rate (HDR) brachytherapy were included in this study. Six plans were created for each of the 4 HDR brachytherapy fractions for each patient: 1 manually optimized and 5 inversely planned. Three of these were based on inverse planning simulated annealing (IPSA) with and without extra constraints on maximum doses of the target volume, and different constraints on doses to the organs at risk (OARs). In addition there were two plans based on dose to target surface points. The resulting dose-volume histograms were analyzed and compared from the dosimetric point of view by quantifying specific dosimetric parameters, such as clinical target volume (CTV) D_{90}, CTV D_{100}, conformal index (COIN), and $D_{2cm}3$ for rectum, bladder and the sigmoid colon.

Results. Manual optimization led to a mean target coverage of 78.3% compared to 87.5%, 91.7% and 82.5% with the three IPSA approaches ($p < 0.001$). Similar COIN values for manual and inverse optimization were found. The manual optimization led to better results with respect to the dose to the OARs expressed as $D_{2cm}3$. Overall, the best results were obtained with manual optimization and IPSA plans with volumetric constraints including maximum doses to the target volume.

Conclusions. Dosimetric evaluation of manual and inverse optimization approaches is indicating the potential of IPSA for brachytherapy of cervical cancer. IPSA with constraints of maximum doses to the target volume is closer related to manual optimization than plans with constraints only to minimum dose to the target volume and maximum doses to OARs. IPSA plans with proper constraints performed better than those based on dose to target surface points and manually optimized plans.

Cervical cancer is a common form of cancer among women worldwide, where about 85% of all incidents occur in developing countries [1]. The resistance to treatment as well as the partial response leading to loco-regional recurrences constitutes significant problems for the treatment of this form of cancer. From this perspective it is crucially important to explore treatment approaches that may improve the treatment outcome. Curative radiotherapy combined with chemotherapy is the standard treatment approach for advanced and inoperable cervical cancers. It is usually performed as external beam radiotherapy (EBRT) combined with a boost of intracavitary brachytherapy (ICBT). The availability of computed tomography (CT) or magnetic resonance imaging (MRI), as basis for computerized three-dimensional (3D) treatment planning in BT, can provide detailed information regarding tumor dose coverage and doses to nearby organs at risk (OARs). Different treatment plans tailored to each

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individual patient, could thus be designed according to the optimization approaches, objectives and constraints used.

This study aims to compare treatment plans for the BT boost performed with 3D inverse optimization to manual optimization (MO). An inverse planning simulated annealing (IPSA) algorithm in the treatment planning system Oncentra MasterPlan is used for optimization of the dose distribution based on given constraints. There are studies comparing the inverse planning for BT of cervical cancer with the MO with respect to dose and volume parameters showing that inverse planning might be superior with respect to normal tissue sparing and at the same time results in comparable target coverage (TC) [2,3]. These studies were mainly focused on comparing standard or MO plans with inverse optimized plans for a subset of tandem or ovoid cases and interstitial template BT. However, they did not address the question of the dose objectives needed to maximize the performance of plans obtained with inverse optimization. Therefore, it is highly relevant to find such a golden standard, or at least, to find a good starting point for final optimization, which should be available to clinics with access to the IPSA algorithm. It was therefore the aim of our study to compare MO plans with five different sets of fixed dose objective parameters forming together five inverse treatment plan approaches. From this perspective, the present study will add to the results reported by Jamema et al. [4] and show the importance of target size when choosing an inverse optimization approach in tandem and ovoid cases.

Material and methods

Patients and treatment

Eighteen patients that underwent RT for cervical cancer during the years 2007–2009 at St. Olav's Hospital, Trondheim, Norway, were included in the study. The stages of the cervical cancers were ranging from IIB to IIIB according to the International Federation of Gynecology and Obstetrics (FIGO) system. Thirteen patients were diagnosed with stage IIB, one with IIIA and four had developed stage IIIB tumors. They all received EBRT based on a four-field box technique ($2\ \text{Gy} \times 25 = 50\ \text{Gy}$) and a boost of 4 fractions of high dose rate (HDR) ICBT with a prescribed fraction dose of 5 Gy. The patients received 5 radiation fractions a week, and the 4 BT fractions were given twice a week during the two last weeks of the overall radiation treatment period. The total minimum physical prescribed dose of 70 Gy to the target is corresponding to an equivalent dose in 2 Gy per fraction (EQD_2) of 75 Gy with $\alpha/\beta = 10$ Gy. The tolerance doses for the sum of external treatment and BT were 90, 75 and 75 Gy for the bladder, rectum and sigmoid, respectively (EQD_2 with $\alpha/\beta = 3$ Gy) [5,6]. These values are based on the minimum dose to the most exposed 2 cm^3 of the organs equivalent to fraction dose limits of 5.7 Gy for bladder and 4.3 Gy for rectum and sigmoid colon.

The overall treatment time was optimized in order to avoid tumor cell repopulation but allow for the repair of the normal tissue between fractions [7,8]. Due to the fact that differences in tumor size and location of soft tissue in pelvic region could be expected from one BT fraction to another, a new MRI-based ICBT treatment plan was performed for each fraction [2,9]. Needles were not used. The BT was delivered with a Fletcher applicator, Titanium Fletcher-style Applicator Set (flexible geometry) GM11006860, connected to a remote after-loader, GammaMed 12i with ^{192}Ir sources (Varian Medical Systems, Palo Alto, CA, USA). Padding was used to keep the treatment device in the same position for the whole treatment occasion, but also for moving away the vaginal wall from the radioactive source. The frontal urinary bladder wall was also pushed away from the vicinity of the target by post-filling the bladder with 100 ml of 0.9% NaCl solution after catheterization. This was done just before MRI was taken with the applicator inserted and just before the BT treatment to ensure equal bladder filling.

Contouring

The treatment planning for ICBT was performed in Oncentra Nucletron MasterPlan v. 1.5 to 3.3 from Nucletron, an Elekta company. The delineation of volumes of interest was performed based on T2 weighted MRI using a 1.5 T MRI scanner. The target, and bladder, rectum and sigmoid colon as OARs were delineated for each BT session. For the rectum and the sigmoid colon only the adjacent part to the target was delineated as OARs and not the entire organ. The clinical target volume (CTV) follows a variant of the GEC ESTRO, high risk-CTV (HR-CTV) [6]. The CTV used in this study covers the tumor and adjacent tissue accounting for possible spread from upper part of vagina and internal parts of the uterus, e.g. a somewhat larger structure than what GEC ESTRO currently recommends [6].

Treatment planning

For each BT fraction, six treatment plans were generated, one MO, which was given for the actual treatment, and five inversely optimized plans generated later:

1. "Equal dwell time" (EDT), all dwell positions inside the CTV were activated for the same amount of time until the prescribed dose was reached as mean dose to 200 target points randomly distributed on the surface of CTV.
2. "Target points" (TP), differing from the EDT by allowing weighting of the dwell times.

3–5. Three different treatment plans using the simulated annealing algorithm, IPSA, were created (see Table I). The IPSA1 plans have a minimum dose constraint on CTV and maximum constraints on the OARs equal to the planned fractionation regimen. The IPSA2 plans were calculated based on slightly higher dose constraints (allowing more dose) to the OARs. The IPSA3 plans are based on the IPSA1 calculations, with additional constraints on the maximum dose to the target volume.

The IPSA plans differ from the EDT and TP plans, by using inversely optimization with respect to preset dose constraints to OARs, and these restrictions were set assuming that the same part of an OAR is irradiated at all four ICBT occasions. The three inverse-generated treatment plans with IPSA had different weights based on empirical observations. The MO treatment plans, were created based on the TP plans where the active dwell positions were further graphically optimized aiming to fulfill the objectives with respect to TC keeping the doses to the OARs below the given limits.

Plan evaluation

The outcomes of the six different treatment plans were compared from a dosimetric point of view. For the quantitative analysis, the cumulative dose-volume histograms (DVHs) for the target and the OARs were used. In the dosimetric evaluation with respect to the CTV the minimum dose given to 90% of the target volume, D_{90}, the minimum dose to target, D_{100}, and the target volume enveloped by the prescribed dose, V_{100}, were evaluated. The comparison between plans was also performed with respect to the conformal index (COIN) which was calculated as the product between TC and conformity index (CI). CI, TC and COIN were defined based on the following volumes: CTV, CTV_{ref} (the part of CTV receiving the prescribed dose or more) and V_{ref} (the total volume receiving the prescribed dose or more) as:

$$TC = CTV_{ref}/CTV$$
$$CI = CTV_{ref}/V_{ref}$$
$$COIN = TC \times CI$$

Acceptable treatment plans result in COIN values higher than 0.5 [10]. For the OARs, the dose to the most exposed 2 cm^3 volume, $D_{2cm}3$, was determined. Two-sided Wilcoxon signed rank test with a 95% confidence interval was used for all statistical analysis.

Results

A summary of the results showing the average dose and volume parameters for the different treatment plans is given in Table II. CTV ranged from 27 to 196 cm^3, with a mean of 92 ± 37 cm^3. The mean CTV D_{90} was statistically significantly higher for the three IPSA plans than for the MO plans. However, the MO plans resulted in a CTV D_{90} better than both EDT and TP. The ranking of the plans with respect to D_{100} was the same as for D_{90} as could be also seen in Table II. Mean COIN values, given in Table II, showed that the inversely optimized IPSA plans led to comparable results to the MO plans with average values above 0.5. The relationships between TC, CI, and COIN in relation to the volume of CTV are shown in Figure 1. In the upper panel one could observe that the IPSA plans led to superior coverage of the target compared to the MO plans and the

Table I. Dose objectives and weighting factors used for the inverse planning simulated annealing plans.

		Surface				*Volume*	
Plan	*VOI*	*D_{min} (Gy)*	*Minimum dose weight, M_{min}*	*D_{max} (Gy)*	*Maximum dose weight, M_{max}*	*D_{max} (Gy)*	*Maximum dose weight, M_{max}*
IPSA1	CTV	5.0	100	6.0	15		
	Rectum			4.3	100		
	Bladder			5.7	100		
	Sigmoid c.			4.3	100		
IPSA2	CTV	5.0	100	6.0	15		
	Rectum			5.3	100		
	Bladder			7.0	100		
	Sigmoid c.			5.3	100		
IPSA3	CTV	5.0	100	6.0	15	50	10
	Rectum			4.3	100		
	Bladder			5.7	100		
	Sigmoid c.			4.3	100		

Table II. Dose and volume parameters for the manually optimized plan and the inverse planning techniques (average for all fractions). The p-values are given for the inverse planning techniques compared to the manually optimized plans.

	MO	*IPSA1*	*IPSA2*	*IPSA3*	*EDT*	*TP*
Point A dose (Gy)	5.0 ± 1.1	5.5 ± 1.5 (p < 0.001)	6.1 ± 1.8 (p < 0.001)	5.2 ± 1.2 *(p = 0.053)*	4.6 ± 1.0 (p < 0.001)	5.4 ± 1.3 (p < 0.001)
TRAK (cGy)	0.18 ± 0.04	0.20 ± 0.06 (p = 0.003)	0.22 ± 0.06 (p = 0.003)	0.19 ± 0.04 (p = 0.016)	0.16 ± 0.04 (p = 0.008)	0.19 ± 0.05 *(p = 0.062)*
CTV: V100 (%)	78.3 ± 8.5	87.5 ± 7.9 (p < 0.001)	91.7 ± 6.0 (p < 0.001)	82.5 ± 9.6 (p < 0.001)	64.8 ± 9.3 (p < 0.001)	74.2 ± 6.7 (p = 0.003)
CTV: V200 (%)	24.4 ± 5.6	29.4 ± 6.6 (p < 0.001)	34.6 ± 7.2 (p < 0.001)	26.4 ± 6.5 (p = 0.009)	22.5 ± 4.8 *(p = 0.211)*	27.1 ± 3.5 (p = 0.003)
CTV: D90 (Gy)	4.1 ± 0.7	4.8 ± 0.7 (p < 0.001)	5.2 ± 0.7 (p < 0.001)	4.4 ± 0.8 (p < 0.001)	3.2 ± 0.5 (p < 0.001)	3.7 ± 0.5 (p < 0.001)
CTV: D100 (Gy)	2.1 ± 0.5	2.6 ± 0.6 (p < 0.001)	2.9 ± 0.7 (p < 0.001)	2.4 ± 0.7 (p < 0.001)	1.7 ± 0.4 (p < 0.001)	2.0 ± 0.5 (p = 0.001)
COIN	0.59 ± 0.08	0.57 ± 0.07 (p = 0.011)	0.55 ± 0.07 (p < 0.001)	0.58 ± 0.07 *(p = 0.125)*	0.50 ± 0.07 (p < 0.001)	0.57 ± 0.07 (p = 0.014)
Bladder$D_{2cm}3$ (Gy)	4.8 ± 0.6	5.1 ± 0.5 (p < 0.001)	5.5 ± 0.6 (p < 0.001)	4.8 ± 0.6 *(p = 0.295)*	4.9 ± 1.2 *(p = 0.194)*	5.0 ± 0.9 *(p = 0.084)*
Rectum$D_{2cm}3$ (Gy)	3.1 ± 0.7	3.4 ± 0.6 (p < 0.001)	3.7 ± 0.7 (p < 0.001)	3.2 ± 0.5 *(p = 0.063)*	2.5 ± 0.7 (p < 0.001)	2.5 ± 0.6 (p < 0.001)
Sigmoid $cD_{2cm}3$ (Gy)	3.7 ± 0.6	4.0 ± 0.7 (p < 0.001)	4.4 ± 0.7 (p < 0.001)	3.8 ± 0.7 (p = 0.023)	3.2 ± 0.8 (p < 0.001)	3.7 ± 0.84 *(p = 0.319)*

EDT and TP plans. The TC corresponding to the IPSA1, IPSA2 and EDT plans showed negligible dependence of the size of the CTV. For the MO and IPSA3 plans the coverage of the target presented a slight decrease with the increase in the size of the CTV while the TP plans seemed to cover better the larger targets. The middle panel of Figure 1 indicates that the CI increase with the increase in size of the CTV for all the plan types. The lower panel of Figure 1 shows that for large volumes, the MO appears to be better with respect to COIN. EDT planning rendered the lowest COIN values independent of volume of the CTV. In addition to Figure 1, a more detailed presentation of the data from which the regression curves for TC and COIN were derived is available as Supplementary Figures 1 and 2 (available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.928829). Supplementary Figure 1 (available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.928829) indicates the advantage of high D90 for IPSA1 and IPSA2 plans compared to IPSA3 and MO plans. However, in Table II the COIN values for IPSA 3 are nearly equal to the MO plans, but higher than for IPSA1 and IPSA2. Table II summarizes the results of CTV V_{200}, dose to point A and Total Reference Air Kerma, TRAK. The differences between the corresponding parameters resulting from the IPSA, EDT and TP plans compared to the MO ones were statistically significant for the majority of the cases, as indicated by the p-values.

For the bladder and the sigmoid colon there was a slight tendency for the $D_{2cm}{}^3$ to increase with CTV D_{90} for both inversely and MO treatment plans, with the steepest relationship being observed for the EDT plans. However, for the rectum it appears that all planning approaches manage to decrease $D_{2cm}{}^3$ with CTV D_{90}. By analyzing all the panels in Figure 2 it appears that IPSA3 plans rendered the results closest to the MO plans.

Discussion

The aim of this study was to evaluate different inverse BT treatment planning approaches available in Oncentra MasterPlan and compare them to the MO treatment planning that is currently performed at St. Olavs Hospital, Trondheim, Norway. The inverse treatment planning using the IPSA algorithm with suitable constraints was found to be a good alternative to the manual planning in terms of TC. This was found to be in agreement with other studies using the IPSA module for intracavitary/interstitial pulsed dose rate/HDR BT for prostate and cervical cancer [2,3,11,12]. The differences between manual and inversely optimized treatment plans may be dependent on target size. In Jamema et al. [2] where target mean size is 41 ± 16 cm^3, compared to our study with a target mean size of 92 ± 37 cm^3, there were no statistical differences in target parameters CTV D_{90} and CTV V_{100} when comparing inverse and manually optimization. The values reported in Table II shows that these target parameters were significantly higher for the IPSA plans compared to MO treatment plans. This result reflects the importance of having several approaches when creating inverse treatment plans, but also to apply these inverse treatment planning approaches to a wider range of clinical cases when evaluating them.

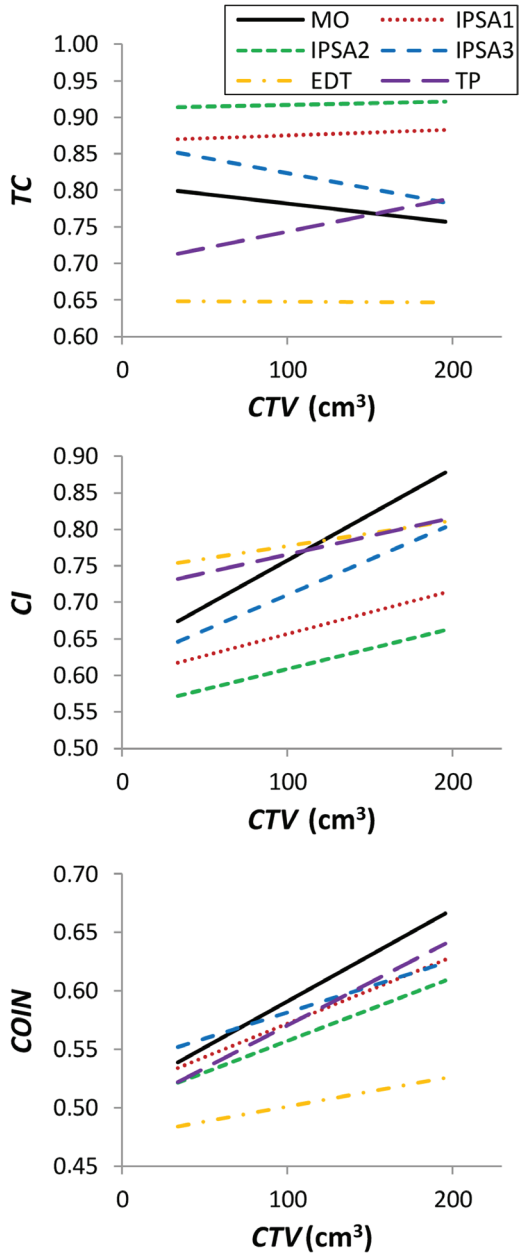

Figure 1. Treatment plan comparison of the dosimetric parameters used in treatment plan evaluation, TC, CI and COIN with respect to CTV. The values obtained for each optimization method are shown as linear regression lines for comparison reasons.

The IPSA plans and the other two inversely optimized plans, EDT and TP, resulted in rather different dose distributions reflected by the parameters investigated in this study due to the fact that they are based on different underlying approaches. The loading patterns in EDT and TP were not considering doses to OARs in their algorithms, the only restriction being that the target surface mean dose should equal 5 Gy. However, TP seemed to be a better choice compared to EDT. For the TP plans the dwelling times for the actual source positions were weighted to adjust the spatial distribution of the dose points on the surface of the CTV, and the dosimetric and volumetric results were reflected by a more stable nature. When the dwelling is equally distributed throughout all the active dwell positions, as for the EDT plans, a slightly off-centered applicator might lead to a mean value of 5 Gy with large deviations within the dose points on the surface of the CTV causing variant results. The difference between EDT and TP indicates that the most difficult target region to be covered by the prescribed dose using surface CTV dose point optimization was towards the proximal part of the intrauterine tandem since a large increase of sigmoid dose was seen in TP versus EDT compared to similar values seen for the rectum and the bladder.

The IPSA module is, with the given inputs, adjusting dwell weights in order to cover the tumor while normal delineated tissues are spared from doses larger than their respective dose limits. When the $D_{2cm}3$ of the OARs were investigated for the IPSA3 plans, they were similar to those resulted from manual planning except for the sigmoid colon where the dose was significantly smaller. Other studies with delineation of HR-CTV according to GEC ESTRO, have also shown difficulties respecting the dose limits to the sigmoid colon [4,13].

The sparing of normal tissue in terms of CI was better for the three treatment planning approaches: MO, EDT and TP compared to the three IPSA approaches. When the IPSA algorithm was first used, the dose constraints and objectives were the ones recommended from Gyn GEC ESTRO (IPSA1). Another treatment plan, IPSA2, was created with slightly less restrictions on doses to OARs. When evaluating the IPSA1 and IPSA2 plans a large inhomogeneity was found in the distribution of dwell positions forming in some cases hot-spots. In an attempt to force IPSA to use a higher number of dwell positions, in hot spot reduction purpose [14], a maximum dose to the target was set to 50 Gy with a small weight of 10 in order to prevent compromising the TC (IPSA3). The other objectives and constraints were the same as for IPSA1. A maximum dose constrain to the target has clearly shown a positive effect on the results when using IPSA. While the dose enveloping of the target is important, this must be achieved without compromising the treatment outcome with OAR complications. Therefore, the irradiation of normal tissue is evaluated together with TC in the form of COIN. CI is the ratio of the volume inside CTV and the total volume receiving the prescribed dose, but it lacks the specific information regarding the irradiation of the OARs. A study of this index needs to be further evaluated with respect to OARs. As the restrictions used for planning with IPSA specify only the constraints to OARs,

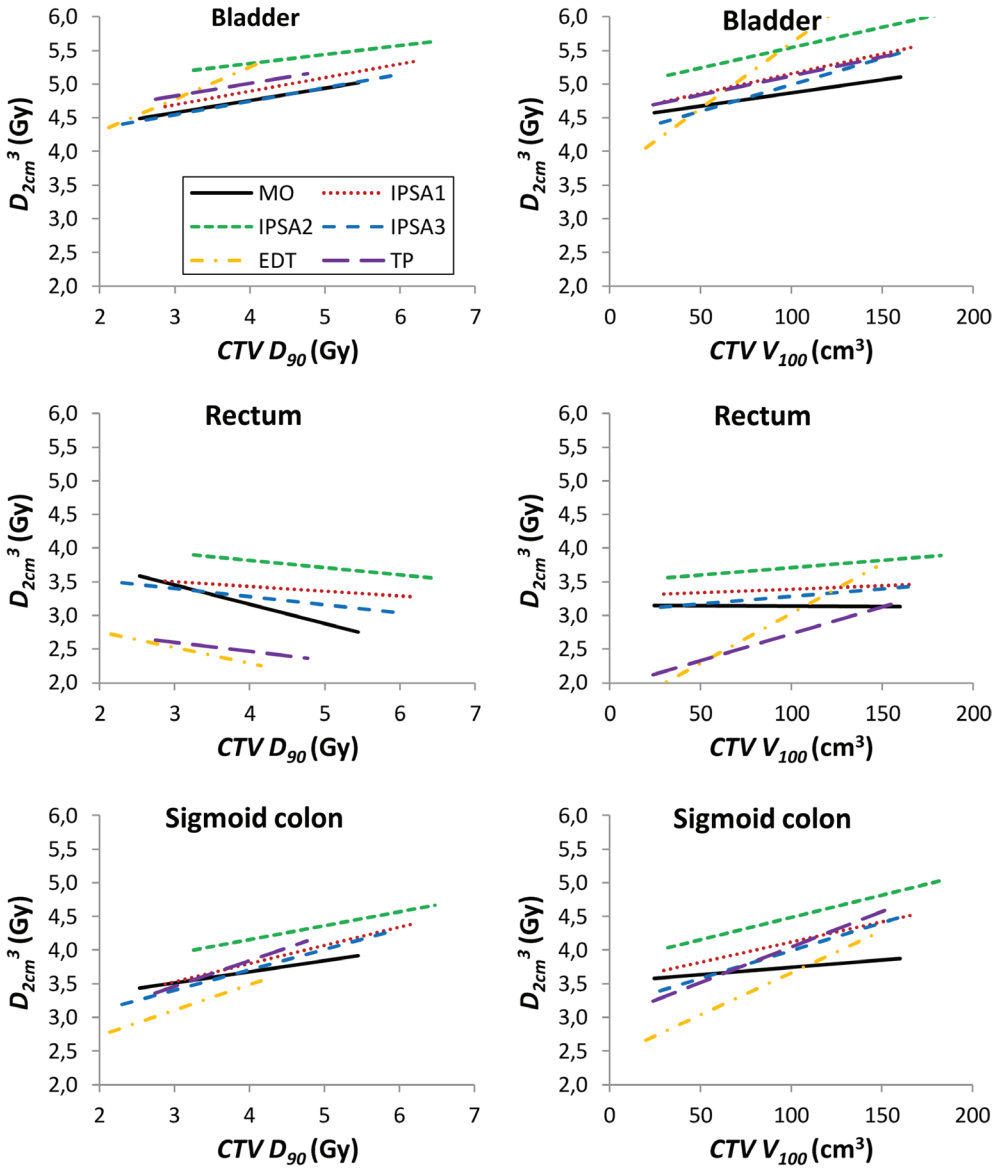

Figure 2. Comparison of the dosimetric parameters OAR $D_{2cm}3$ with respect to CTV D_{90} , left panels, and CTV V_{100}, right panels.

non-delineated volumes, e.g. healthy tissue, might get irradiated on the expenses of good TC. It is therefore of interest to evaluate the different treatment plans in the context of non-delineated tissue. The TC for the IPSA1 and IPSA2 plans seemed not to be affected by the target volume, however in the IPSA3 plans the TC seemed to decrease with increasing target volume. For the largest target volumes the COIN values were higher than for the smallest volumes (for all the treatment optimization plans used) mostly due to a larger CI for these plans. IPSA3 is recommended as the best planning approach accounting for doses to OARs and dose homogeneity, however, for the larger target volumes the TC was lowered for this optimization method. The study by Chajon et al. [9] showed difficulties in obtaining high target volume coverage for large tumors while not compromise the sparing of OARs. IPSA treatment planning with entry constraints based on the evaluation of the dependence of the dosimetric parameters on the CTV volume could therefore be of interest.

To our knowledge this is the only study evaluating different combinations of objectives and OAR constraints using IPSA algorithm for HDR BT of cervical cancer comparing dosimetric indexes for BT fractions. The large number of plans, as a result from individual planning for all fractions for each of the 18 patients, makes the evaluation statistically relevant.

In conclusion, the dosimetric evaluation comparing manual and inverse optimization approaches indicates the potential of inverse planning simulated annealing for BT of cervical cancer. IPSA with constraints of maximum doses to the target volume gives better plans than with constraints only to minimum

dose of the target volume and maximum doses to OARs. IPSA plans with proper constraints might therefore represent better starting points for finalizing the optimization than plans only based on doses to target surface points.

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Supplementary material available online

Supplementary Figures 1–3 available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.928829