Radiobiological Treatment Planning Evaluation of Inverse Planning Simulated Annealing for Cervical Cancer High-dose-rate Brachytherapy

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Abstract. *Aim: To compare five inverse treatment plans with one conventional manually-optimized plan for cervical cancer brachytherapy (BT) using radiobiological parameters combined with dosimetric and volumetric parameters. Materials and Methods: Five inverse treatment plans were calculated using an inverse planning simulated annealing (IPSA) algorithm for each of four fractions for 12 cervical cancer patients treated with high-dose-rate (HDR) brachytherapy. The inverse treatment plans were compared to a manually-optimized plan used for the actual treatment of the patients. The comparison of the plans was performed with respect to the probability of cure without complication (P_+). Results: Overall, the manually optimized plan scored the best results; however, the probability of cure without complication is within an acceptable clinical range for all the plans. Conclusion: Although there are still considerable uncertainties in the radiobiological parameters, the radiobiological plan evaluation method presents itself as a potential complement to physical dosimetric methods.*

Inverse planning algorithms have been emerging in the brachytherapy (BT) setting as alternatives to the manual optimization (MO). However, the various treatment planning tools currently available as alternatives to manual planning very often require tuning based on empirical observations and clinical experience, thus a thorough comparison between the manually and inversely optimized plans is warranted. There are several studies in the literature presenting comparisons between manually and inversely-optimized plans (1-5). The comparison between plans obtained using inverse optimization with the manual planning has so far been performed based on dosimetric and volumetric parameters. A recent study by Palmqvist *et al.* (5) compared five inverse treatment plans against a manually-optimized plan with regard to the above mentioned parameters and concluded that inverse planning simulated annealing (IPSA) with constrains of maximum doses to the target volume may be a feasible alternative to manual optimization with respect to the target coverage and dose to the organs at risk (OARs). However, the relationship between dose and radiobiological and clinical outcomes is not linear. It would, thus, be also interesting to evaluate the plans from a radiobiological point of view in order to determine whether the small differences between plans, in terms of dose and irradiated volumes, would translate into significant differences in probability of controlling the tumour and normal tissue complication probabilities. To the best of our knowledge, there exists no study in which the comparison between inverse planning and manual optimization has been performed with respect to radiobiological parameters combining the volumes and the doses received by either the target or the OARs with parameters describing the sensitivity to radiation of the various tissues involved. Therefore, the aim of the present study is to compare manually optimized plans with inverse treatment planning previously reported by Palmqvist *et al.* (5) from a radiobiological point of view. Specifically, the aim of this retrospective study was to compare five inverse treatment plans against a manually-optimized plan using the radiobiological parameter P_+ describing the probability of cure without complication.

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Table I. *Optimization parameters used in the IPSA plans.*

IPSA plan		Minimum surface dose (Gy)/weight	Maximum surface dose (Gy)/weight	Maximum volume dose (Gy)/weight	Comments
IPSA 1	CTV	5.0/100	6.0/15		High weight imposed for the objective regarding the minimum surface dose in comparison to the maximum surface dose.
	Rectum		4.3/100		
	Bladder		5.7/100		
	Sigmoid c.		4.3/100		
IPSA 2	CTV	5.0/100	6.0/15		The same objectives for CTV as for IPSA 1 plan but higher tolerance doses for the OARs expected to lead to a better target coverage.
	Rectum		5.3/100		
	Bladder		7.0/100		
	Sigmoid c.		5.3/100		
IPSA 3	CTV	5.0/100	6.0/15	50/10	The same objectives as for IPSA 1 plan but limitation with respect to the maximum dose within the CTV for better homogeneity.
	Rectum		4.3/100		
	Bladder		5.7/100		
	Sigmoid c.		4.3/100		

IPSA, Inverse planning simulated annealing; CTV, clinical target volume; OARs, organs at risk.

Table II. *Radiobiological parameters used for the calculation of the probability of cure without complication* P_+.

VOI	D_{50} (Gy)	γ	α/β (Gy)	N_0	SF_2	a
CTV			10	106	0.4	–4
Bladder	80	3.0	5			2
Rectum	75	2.5	5			8
Sigmoid c.	75	2.5	5			8

VOI, Volume of interest; CTV, clinical target volume.

Materials and Methods

Patients and treatment. This study examines the BT treatment plans of 12 patients who suffered from cancer of the cervix and were treated between the years 2007-2009 at St. Olav's Hospital, Trondheim, Norway. According to the International Federation of Gynecology and Obstetrics (FIGO) classification the malignant disease varied from IIB to IIIB. The patients were treated with external beam radiation therapy (EBRT) (2 Gy×25=50 Gy) and a boost of high-dose-rate intracavitary brachytherapy (HDR ICBT) (5 Gy×4=20 Gy) resulting into a total minimum physical prescribed dose to the tumour corresponding to a biological equivalent dose in 2 Gy per fraction (EQD2) of 75 Gy_{EQD2} (α/β=10 Gy). The OARs tolerances for EBRT+BT were 90 Gy_{EQD2} for the bladder and 75 Gy_{EQD2} for rectum and sigmoid (α/β=3 Gy) (6, 7). The full portrayal of the treatment received by the patients has been described (5).

Treatment planning. For each of the 12 patients, six different plans were produced for each BT treatment fraction as described elsewhere (5). In addition to the MO plan that was actually used for treating the patients, five inversely optimized plans were retrospectively generated: (i) equal dwell time (EDT) plan allowing for the same amount of time for all active positions inside the CTV, the prescribed dose was reached as mean dose to 200 target points randomly distributed at the surface of CTV, (ii) target points (TP) plan differing from EDT by allowing weighting of dwell time, and (iii-v) three plans using inverse simulated annealing algorithm (IPSA). A short description of the parameters used for optimization in the IPSA plans is given in Table I.

For the EBRT, two plans were considered, one based on a four-field box technique and one intensity modulated (IMRT) plan with constraints for the dose to OARs.

Plan evaluation. The evaluation of the plans and the subsequent comparison was performed with respect to a hybrid radiobiological parameter introduced by Ågren *et al*. (8, 9) as the probability of cure without complication, P_+, given by equation 1:

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

where *TCP* is the tumour control probability, *NTCP* is the normal tissue complication probability for a specific OAR and δ is a parameter indicating the degree by which the probability of controlling the tumour and the normal tissue complication probability could be considered statistically independent (8, 9). In this study, δ was assumed to be 0.2 as suggested by Ågren *et al*. (8, 9).

TCP and *NTCP* were calculated using the generalized equivalent uniform dose in 2 Gy per fraction $gEUD_2$, which is the general equivalent uniform dose (*gEUD*) calculated for equivalent dose in 2 Gy fractions (EQD2) (10-12).

Thus, if the treatment was performed using a different dose per fraction than the standard 2 Gy, one could calculate the equivalent dose in 2 Gy fractions (EQD2). Assuming the linear-quadratic (*LQ*) model for cell killing, the EQD2 could be calculated using equation 2:

Table III. *The difference between the P_+ for each of the inverse plans and the corresponding manually optimized plan. The P_+ was calculated based on the tumor control probability and the normal tissue complication probability for each OAR (bladder, rectum or the sigmoid colon). The total dose was calculated assuming that the external radiotherapy was delivered as conventional four-field technique or IMRT. Method 1and method 2 were both used for calculation of $gEUD_2$.*

$\Delta P_+ = P_{+INV} - P_{+MO}$						
Method 1						
OAR	*EBRT*	*IPSA1*	*IPSA2*	*IPSA3*	*EDT*	*TP*
Bladder	*CRT*	–0.6±0.6	–1.4±1.2	–0.3±0.4	–0.2±0.3	–0.2±0.4
	IMRT	0.4±0.3	0.0±0.5	0.5±0.2	0.6±0.2	0.6±0.3
Rectum	*CRT*	0.0±6.7	–6.8±4.0	1.9±7.1	7.5±11	7.6±11
	IMRT	0.1±6.7	–6.7±4.0	1.9±7.1	7.6±11	7.6±11
Sigmoid c.	*CRT*	–5.1±5.9	–14.6±8.1	–1.3±6.0	1.7±17	–5.8±11
	IMRT	–6.1±6.0	–15.7±8.2	–2.2±6.0	0.9±17	–6.8±11
Method 2						
Bladder	*CRT*	–0.5±0.4	–0.9±0.8	–0.2±0.2	0.0±0.2	–0.1±0.2
	IMRT	–0.5±0.5	–1.0±0.9	–0.3±0.3	–0.1±0.2	–0.1±0.3
Rectum	*CRT*	–1.5±5.5	–8.1±3.7	0.6±5.9	7.6±9.4	7.8±8.9
	IMRT	–2.4±5.4	–9.1±3.7	–0.2±5.8	7.0±9.4	7.2±8.8
Sigmoid c.	*CRT*	–4.0±3.5	–10.6±5.0	–1.4±3.4	1.6±9.3	–3.1±6.7
	IMRT	–5.0±3.6	–11.6±5.1	–2.3±3.5	0.9±9.5	–4.0±6.9

EBRT, External beam radiation therapy; CRT, conformal radiation therapy; IMRT, intensity modulated radiation therapy; IPSA, inverse planning simulated annealing; EDT, equal dwell time; TP, target points.

$$EQD_2 = D \cdot \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

where D is the total physical dose, d is the dose per fraction and α/β is the dose were the linear contribution to damage equals the quadratic contribution (in the *LQ* model).

Furthermore, for a treatment plan resulting in a heterogeneous dose distribution over the tumour or the OARs, the *gEUD*, which is the generalized equivalent uniform dose that gives the same biological effect as a heterogeneous dose distribution, is given by equation 3:

$$gEUD = \left(\frac{1}{N}\sum_{i=1}^{N} d_i^a\right)^{\frac{1}{a}}$$

where N is the number of voxels in each organ, d_i is dose in the voxel, a is a parameter describing the response of the structure or organ in relation to the irradiated volume; $\alpha<0$ for tumours where cold spots are unwanted and $\alpha>0$ for healthy tissue where one should pay attention to hotspots.

For the complex scenario, where the dose is delivered in a dose per fraction d and the resulting treatment plan is described by the corresponding dose volume histograms (DVHs) for the target and the OARs, one could use two methods for the calculation of $gEUD_2$.

Method 1 employs first the calculation of EQD2 for each bin in the DVH using equation 2 and subsequently the calculation of the corresponding $gEUD_2$ using equation 3 in which N is the number of bins in the DVH.

Method 2 employs first the conversion of the heterogeneous dose distribution described by the DVH into the corresponding *gEUD* for the actual dose per fraction using equation 3 followed by the calculation of $gEUD_2$ using equation 2 in which the dose D is in fact the *gEUD* resulting from the DVH.

As the two methods for the calculation of $gEUD_2$ are expected to render different results (12), none of them being established as the standard calculation procedure in this case, both of them were applied in order to verify if the calculation method for the $gEUD_2$ will influence the ranking of the inversely optimized plans relative to the MO plan with respect to P_+.

For each of the 12 patients and the six BT plans, the DVHs were converted into $(gEUD_2)_{BT}$. The contribution of the EBRT plans was also taken into account by calculating the corresponding $(gEUD_2)_{EBRT}$. Using the fact that $gEUD_2$ is an additive quantity, the total equivalent uniform dose in 2 Gy per fraction for each patient was calculated as the sum of $(gEUD_2)_{BT}$ and $(gEUD_2)_{EBRT}$.

Assuming the *LQ* model for cell killing and Poisson statistics, *TCP* is calculated as described by equation 4:

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

where N_0 is the initial number of clonogenic cells in the tumour, SF_2 is the surviving fraction at 2 Gy and D is the calculated $gEUD_2$ total dose for the tumor.

The *NTCP* was calculated using a logistic model, which is given by equation 5:

$$NTCP = \left[1 + \left(\frac{D_{50}}{D}\right)^{4\gamma}\right]^{-1}$$

where D_{50} is the uniform organ dose that gives 50% response, γ is the maximum normalized dose response gradient and D is the calculated $gEUD_2$ for OARs.

The radiobiological parameters used in the calculations are given in table II (9, 12-15).

Thus, the probability of cure without complication, P_+, was calculated for each of the 12 patients, for all six BT plans in combination with either the plan resulting from the four-field box technique or the IMRT plan for the EBRT.

For each of the above combinations of plans, six sets of values were calculated corresponding to the two methods for calculating the $gEUD_2$ and to one of the three OARs at a time.

Finally, the average P_+ for all patients was calculated. As the ultimate aim of the study was the ranking of the BT plans relative to the MO plan, the actual absolute P_+ values were of limited interest. Therefore, the results are reported as percentual differences between the P_+ for the inverse plans and the corresponding MO.

Results

The comparison between plans with respect to the values of the probability of cure without complication, P_+, corresponding to Method 1 and Method 2 for calculating $gEUD_2$ is shown in Table III. The differences in P_+ for each of the inverse plans and the corresponding manual optimized plan were calculated based on the *TCP* and the *NTCP* either for the bladder, rectum or sigmoid colon. The total dose was calculated assuming that the external beam radiotherapy was delivered either as conventional four-field technique or as IMRT.

Thus, Table III shows the comparison of the P_+ values between each of the inverse (P_{+INV}) and the manual plan (P_{+MO}) as $\Delta P_+ = P_{+INV} - P_{+MO}$. The two methods for the calculation of $gEUD_2$ and consequently ΔP_+ render very similar values.

The actual differences in P_+ between plans are very small. For instance, the differences in P_+, considering the bladder as the critical organ at risk, are up to 1 % for all the planning approaches. This proves that the differences in the physical parameters do not translate into considerable differences in the radiobiological parameters. For the rectum, the differences in P_+ are higher but still below 10%. It appears that the decrease in the dose to the rectum resulting from the EDT and TP plans would decrease the normal tissue complication probability, thus leading to a higher P_+ for these plans in comparison to the manually optimized ones. The largest differences in P_+ are observed for the sigmoid colon for the IPSA2 plan. This is not a surprising result since IPSA2 admits higher doses for the OARs.

Discussion

To the best of our knowledge, this is the first attempt to make a comparison based on radiobiological parameters between treatment approaches including BT and EBRT. The previous study by Palmqvist *et al*. (5) ranked the treatment plans using dosimetric parameters. It was the aim of this paper to assess if the ranking of the inversely optimized plans relative to the MO plan will be the same if the radiobiological concept P_+ was used.

Scarce information available in the literature on the radiobiological parameters to be used for the calculation of P_+ may lead to uncertainties in the actual values for the probability of cure without complication. The robustness of the results with respect to the uncertainty in the δ-parameter representing the statistically-independent fraction for tumor and normal tissue responses has been tested by performing the calculations using a broad range of δ values between 0 and 20%. The results did not show any significant dependence on the choice of δ because of the large differences between the absolute values of the *TCP* and *NTCP*. However, as the aim of our study was not to determine the absolute values of P_+ but to rank the inversely optimized plans according to these values, the uncertainties in the radiobiological parameters used for the P_+ calculations may not play a critical role.

It should be noted that the patients reported in this study underwent EBRT with a four-field box technique, where, in some cases, OARs were more irradiated compared to other EBRT techniques like IMRT (16). Therefore, even if the planning target volume (PTV) in EBRT includes OARs, for BT, the reduction of dose to a highly sensitive serial type OAR like the bone marrow could be of great importance for the clinical outcome or if the patient is in need of another treatment that includes dose to pre-irradiated OARs.

Among the inverse treatment plans, IPSA3 was deemed to be the closest competitor of the MO method. Thus, EDT seems to be the next competitor; however, the significant deviations in the P_+ to the sigmoid colon should be carefully noted.

The concept of *gEUD* was devised to circumvent the heterogeneous dose distributions and dose gradients from the IMRT treatment plans (10, 17). The steep dose gradients characteristics observed in cervical cancer BT and IMRT can be similar; therefore, the *gEUD* formalism can also apply to this BT study. The calculation of $gEUD_2$ with Methods 1 and 2 yielded different results; however, the relative ranking of the treatment plans with respect to P_+ is invariant regardless of the method employed. The dosimetric method produced the same hierarchy of the plans (5). Method 1 is a better choice when the radiobiological parameters describing radiosensitivity of volumes of interest (VOIs) are available and if they give the dose to voxels instead of DVHs (12).

A radiobiological evaluation of treatment plans has been presented. Despite uncertainties inherent to radiobiological parameters, the order of classification of the treatment plans with regard to P_+ is in concordance with results acquired using dosimetric parameters previously reported. The radiobiological method has, therefore, the potential to be a viable complement to dosimetric methods.

Conflicts of Interest

None to declare.

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