

Use of a correlation analysis model in the optimization of intensity-modulated radiotherapy of prostate cancer

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Abstract. The aim of the present study was to develop a statistical model-based method for the optimization of intensity-modulated radiotherapy (IMRT). A prostate cancer IMRT plan was redesigned while retaining the same beam orientation and prescribed dose as the regular plan. A series of dosimetric parameters were generated, and a 4-step protocol was performed to analyze the data: i) The tumor control probability of the target was ensured by setting a number of strict constraint parameters so that much of the target was covered by the 95% isodose line; ii) the parameters for optimization [weight ratio, equivalent characteristic parameter a and maximum equivalent uniform dose of the organ at risk (OAR)] were adjusted; iii) the overall optimization space (OOS) was determined via analysis of the dose-parameter tables based on the correlation factor (CF) and optimization efficiency factor analysis; iv) the OOS in the Pinnacle V_{7.6} treatment planning system with IMRT function was transposed. A selected optimization phenomenon existed when different optimization methods were used to optimize dose distribution to the targets and OARs, which demonstrates a wide variation in the CFs between the percentage of planning target volume receiving 95% of the prescribed dose and the maximum dose of the bladder, rectum and femur. The OOS used to optimize the randomly selected plan exhibited relatively high efficiency, with benefits for the optimization of IMRT plans. For patients with prostate cancer who require complex IMRT plan optimization, the obtained OOS from the two core analysis techniques

is likely to have relatively high efficiency in achieving an optimized plan. These results suggest that the correlation analysis model is a novel method for the optimization of IMRT for prostate cancer.

Introduction

Prostate cancer is one of the leading causes of cancer-related mortality in men worldwide. It has been estimated that ~218,000 men were diagnosed with prostate cancer in the United States in 2010, while >32,000 succumbed to the disease (1). Intensity-modulated radiotherapy (IMRT) and image-guided source placement (2) are often used in the treatment of prostate cancer. IMRT has widened the horizons of radiation therapy due to its ability to conform radiation dose distributions to complex tumor target volumes while sparing nearby critical structures as much as physically possible. The use of IMRT to treat prostate cancer improves the overall survival and disease-free survival rates (3). Furthermore, compared with traditional three-dimensional conformal radiotherapy, IMRT improves normal tissue sparing in prostate cancer therapy, without compromising the dose delivered to the target (4). To be effective, however, the implementation of IMRT requires accurate targeting of the prostate and the selection of appropriate treatment parameters.

Wu Q *et al* (4) used equivalent uniform dose (EUD)-based optimization to obtain intensity-modulated radiotherapy plans for prostate and head-and-neck cancer patients and compared them with the corresponding plans optimized with dose-volume-based criteria. Joo *et al* (5) conducted a retrospective study, which indicated that in response to whole pelvic IMRT (44-46 Gy with a boost of up to 76 Gy) without using the EUD-based optimization method to protect the surrounding normal tissue, 73% of patients exhibited acute genitourinary toxicity. A similar study compared plans with different optimization parameters for the organ at risk (OAR), while the overall target objective function was constrained to -10 (6). In addition, a study by Leung *et al* (7) indicated that setting the ECPa to a value of 1 could significantly reduce the parotid irradiated volume dose (V_x) in the treatment of head and neck cancer; however, the parameter optimization of the targets and OARs was not clear. The aim of the present study was to investigate a new statistical model-based parameter optimiza-

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Table I. Model-based statistical analysis.

OM	a_1	a_2	a_j	a_n			
	Optimization Results				OF	CF	OOS
Key end	f_{k1}	f_{k2}	f_{kj}	f_{kn}	OF_k	1	MOR_k
Non-key end							
1	f_{11}	f_{12}	f_{1j}	f_{1n}	OF_1	CF_1	MOR_1
2	f_{21}	f_{22}	f_{2j}	f_{2n}	OF_2	CF_2	MOR_2
3	f_{i1}	f_{i2}	f_{ij}	f_{in}	OF_i	CF_i	MOR_i
4	f_{n1}	f_{n2}	f_{nj}	f_{nn}	OF_n	CF_n	MOR_n

OM, optimization method; OF, optimization factor; CF, correlation coefficient; MOR, most optimum region; OOS, overall optimization space.

tion method (OM) for IMRT planning, which may facilitate the development of a superior IMRT plan.

Materials and methods

Establishment of the statistical model-based analysis. The OM in Table I included 3 steps: i) Optimize 'wf_i'; ii) optimize the constraint dose, which consists of both the point dose constraint and the EUD constraint; iii) report the dose-volume constraint or dose-volume histogram-based optimization. OM refers to one of the OMs mentioned above. Accordingly, $a_i \in OM$ represented one optimization parameter term of OM.

In the present analysis model, each OM led to definitive results for both the targets and OARs. f_i represented the *i*th result due to a certain OM, and f_k was defined as a dosimetric requirement that had to be firstly satisfied. f_k was highly associated with the outcome of the radiotherapy and the treatment objective, representing a minimum target control dose in curative treatment situations and a maximum OAR tolerance dose in palliative treatment situations. Based on our theory, it was assumed that only one f_k existed in all relevant results and that f_i optimization should only be performed when the f_k constraint was absolutely satisfied. f_{ij} represented a sub-optimized result of the *i*th result of f_i by the *j*th selected optimization parameter belonging to the OM. Each f_i was a function of a certain OM. The Excel 'Linest' function was thus employed to adapt the data into a least-squares fitting model, and the following equation was obtained: $f_i = F_i(OM) = OF(a_i) + \chi$. In this equation, the fitting factor 'OF' is representative of the influence effort that leads to a variation in the optimization parameter, i.e. the optimization factor. The value OF_i is the influence effort that is caused by the OM.

The Slope of Approximate Linear Fitting function is defined as OF. Thus, by using the function analysis method, the approximate slope of the effective coefficient optimization was obtained with the Series function slope formula (7):

$$OF = m = \frac{n(\sum \bar{x} \cdot \bar{y}) - (\sum \bar{y} \cdot \sum \bar{x})}{n(\sum \bar{x}^2) - \sum \bar{y}^2}$$

The following definition about the efficiency of the OF was established: OF < 0 indicates an opposing optimization effort; OF = 0 indicates an invalid optimization effort; 0 < OF < 1 indicates a weak, valid optimization effort; and OF > 1 indicates a powerful optimization effort.

The correlation factor (CF) refers to the statistical correlation factor between f_i and f_k , $CF \in [-1, 1]$. CF represents the level of correlation between any two data sets. For any two f_i and f_k , there exist pairs of CFs according to the law of the Pearson correlation coefficient (8):

$$CF_i = r_{x,y} = \frac{\sum (x - \bar{x})(y - \bar{y})}{\sqrt{\sum (x - \bar{x})^2 \sum (y - \bar{y})^2}}$$

We therefore attempted to investigate whether any dosimetric improvement in the f_i of the non-key results would cause a dosimetric deterioration of f_k according to this analysis. CF analysis is only recommended between f_i and f_k . For the presupposition model, the treatment objective result was only led by the key result f_k . Similarly, the definition of the CF in different situations was established: CF = 0, no correlation between f_i and f_k ; CF < 0, negative trend of two data sets; CF > 0, positive trend of two data sets.

The most optimal region (MOR) refers to one of the optimization elements of the parameter aggregate of OM, which produces the most optimal results for f_i . In order to facilitate the identification of the MOR in the present study, it was defined as a closed region for MOR_k of f_k , and a single value for MOR_i of f_i . Thus, the overall optimization space (OOS) was defined, as follows: $OOS_{OM(i)} = \{MOR_k, MOR_1, MOR_2, \dots, MOR_i, MOR_n\}$. Clearly, it has C_n^m types of OOS in cases of N numbers of optimization parameters with M types of optimized results.

Optimization logic. First, consider the MOR_k , which was a closed interval. The optimization parameter, which was the treatment objective-related tolerance dose for the OAR or the minimum target dose, was $[f_{km}, f_{kn}] \rightarrow [a_{km}, a_{kn}]$. Secondly, if $CF_i \geq 0.5$, and there was $\geq 50\%$ correlation between f_i and f_k , the interval selection of MOR_i was the value that made f_i optimum in the closed interval $[a_{km}, a_{kn}]$. Thirdly, if $CF_i < 0.5$ and the relatively smaller CF existed between the two results,

Table II. Setting of optimization parameters for physical and biological dose constraints.

Type	PTV objective				OAR objective		
	minDose	maxDose	minDVH	minEUD	Bladder maxEUD ₀ ^a	Rectum maxEUD ₀	Femur maxEUD ₀
Dose (Gy)	69.0	73.5	70.5	69.0	20	20	20
Weight	40	40	40	40	1	1	1
ECPa	-	-	-	-50	1	1	1

^amaxEUD₀=20 Gy. PTV, planning target volume; OAR, organ at risk; DVH, dose-volume histogram; EUD, equivalent uniform dose; ECPa, equivalent characteristic parameter; maxDose, maximum dose; minDose, minimum dose.

Table III. Dosimetric parameters of the targets and organs at risk in the ECPa optimization method.

ECPa	Vx (v ₉₅) (v ₄₀) (v ₁₅)				maxDose			meanDose		
	F-PTV	F-bladder	F-rectum	F-femur	F-bladder	F-rectum	F-femur	F-bladder	F-rectum	F-femur
CF	1.000	-0.197	-0.530	0.835	0.895	0.906	0.721	0.330	0.120	0.340
OF	-0.00820	0.000195	0.00365	-0.00240	-38.1	-37.1	-35.2	-3.29	0.140	-3.88
MOR	-50	1	1	7	7	7	7	1	1	3

OF, optimization factor; CF, correlation coefficient; MOR, most optimum region; ECPa, equivalent characteristic parameter; PTV, planning target volume; Vx, volume dose; maxDose, maximum dose; meanDose, mean dose; F, factor.

then the interaction between f_i and f_k could be neglected, but the optimization efficiency factor had to be taken into account. Fourthly, although the CF may be relatively low, it could actually have an effect on the optimization efforts to f_i . This step shows partiality for the selection of f_i and will accordingly have an improved optimal end value for f_i . Fifthly, if $0.5 > OF_i > 0$, the selection of MOR_{*i*} from the set of $[a_m, a_n]$ will push f_i to an optimum. Similarly, if there is a small CF, and the optimization efficiency factor was also shown to be at a minimum, there should be an attempt to obtain a satisfactory result for f_k .

A prostate cancer patient plan was randomly selected to demonstrate the application of the statistical analysis as an optimization theory. The plan was redesigned using an inverse planning system [Pinnacle treatment planning system (TPS), version 7.6; Philips Medical Systems, Fitchburg, WI, USA]. The dose-constraint objective function is shown in Table II.

A comparison of the dose distribution of radiation at doses known to cause toxicity in normal tissue was also performed. For the planning target volume (PTV), the percentage of PTV receiving 95% (V₉₅) of the prescribed dose was recorded for comparison. For the OARs (rectum, bladder and femur) the Radiation Therapy Oncology Group protocol tolerance dose limitation (9) was used as a guideline for the specified normal tissue. The constraints were as follows: <40% of the volume of the rectum could receive 55% of the prescribed dose; <40% of the volume of the bladder could receive 55% of the prescribed dose; and <30% of the volume of the femur could receive 20% of the prescribed dose. The maximum and mean doses

(maxDose and meanDose, respectively) of the OARs were also evaluated in this study. All constraints to limit OAR irradiation were made by a single optimization parameter: maxEUD. For the sake of simplicity, the parameter 'a' and weight 'w' were considered equally. All IMRT inverse planning was performed using the same number of beams, and beam arrangements were the same as those used in the initial IMRT plan. The PTV dose constraint objective function optimization parameters were statically maintained. In the first step, the parameter 'a' was independently changed, the definition closed interval of a was [1,50], and the value of the OOS_{om(a)} obtained from the first step was used in the optimization of 'w'. The domain of 'w' was [0.02,1]. The OOS_{om(a)} and OOS_{om(w)} were successfully obtained based on the optimization logic. The next procedure was to calculate the OOS_(maxEUD) through a similar method, by inputting the OOS (OMA) and OOS (OMK) into the initial EUD constraint dose to all OARs, EUD₀ = 1,000 cGy, and then performing the following variation: EUD±100, 300, 500, 700, 900. Based on the above 4-step analysis, the OOS was found for all of the OMs that had been performed. Finally, the OOS was transposed into the IMRT optimization section of the TPS to compare the OOS-guided plan with the initial plan.

Results

Demonstration of optimization efficiency of different dosimetric parameters in the optimization of ECPa. To determine the optimization efficiency of ECPa, the meanDose, maxDose and Vx of the OARs were studied as the ECPa gradually increased. As shown in Fig. 1 and Table III,

Table IV. Dosimetric parameters of targets and organs at risk in the weight 'w' optimization method.

Kw	Vx (v ₉₅) (v ₄₀) (v ₁₅)				maxDose			meanDose		
	F-PTV	F-bladder	F-rectum	F-femur	F-bladder	F-rectum	F-femur	F-bladder	F-rectum	F-femur
CF	1.000	0.988	0.823	0.649	0.450	0.480	0.530	0.928	0.783	-0.244
OF		6.13	8.71	9.81	0.000370	0.00258	0.00396	5.58	4.81	10.5
MOR	40	40	40	40	10	10	10	40	10	40

OF, optimization factor; CF, correlation coefficient; MOR, most optimum region; PTV, planning target volume; Vx, volume dose; maxDose, maximum dose; meanDose, mean dose; F, factor.

Table V. Dosimetric parameters of targets and organs at risk in the maxEUD constraint optimization method.

maxEUD	Vx (v ₉₅) (v ₄₀) (v ₁₅)				maxDose			meanDose		
	F-PTV	F-bladder	F-rectum	F-femur	F-bladder	F-rectum	F-femur	F-bladder	F-rectum	F-femur
CF	1.000	0.967	0.953	0.825	0.971	0.985	0.951	0.870	0.910	0.950
OF		1.29	1.23	1.03	1.39	1.15	1.82	0.86	0.87	0.62
MOR		EUD ₀ ^a +9 Gy	EUD ₀ +9 Gy	EUD ₀ +1 Gy	EUD ₀ +9 Gy	EUD ₀ +9 Gy	EUD ₀ +1 Gy	EUD ₀ +9 Gy	EUD ₀ +9 Gy	EUD ₀ +1 Gy

EUD₀^a=20 Gy. OF, optimization factor; CF, correlation coefficient; MOR, most optimum region; PTV, planning target volume; EUD, equivalent uniform dose; Vx, volume dose; maxDose, maximum dose; meanDose, mean dose; F, factor.

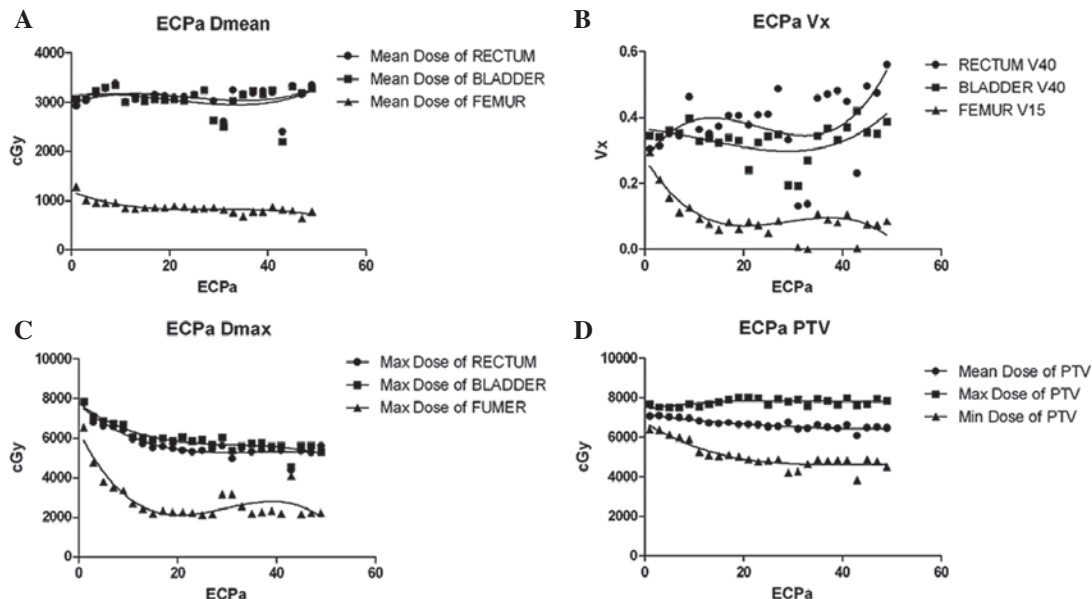


Figure 1. OF of OARs using the ECPa method. (A) Invalid optimization OF <0.01. ECPa has little optimization effect on the Dmean of the OARs. (B) ECPa has little effect on decreasing the irradiated Vx of the bladder. There was a negative optimization effect when ECPa was used to reduce the V₄₀ of the rectum. (C) Efficiency of reducing the hot-point dose of the OARs. The ECPa had a relatively high efficiency in eliminating the hot-point. (D) When OF >1 and the value of 'a' increased from 0 to 20, the Dmax and minimum dose of the PTV showed opposing variation trends. The OF of the ECPa relative to the minimum dose was more powerful than that of the Dmax; therefore, a slightly lower trend of the Dmean of the PTV was observed. All the variation trends of the PTV became more stable when the value of 'a' was >20. OF, optimization factor; OAR, organ at risk; ECPa, equivalent characteristic parameter; Dmean, mean dose; Dmax, maximum dose; Vx, volume dose; PTV, planning target volume.

the ECPa had little effect on decreasing the irradiated Vx of the bladder, and a negative optimization effect was observed when ECPa was used to reduce the V₄₀ of the rectum. This

may have been due to the following reasons: i) There was an overlap between the rectum and the PTV, which was unsuitably defined; and ii) the numeric optimization algorithm

Table VI. Overall optimization space to different optimization methods (EUD₀=20 Gy).

OM	PTV	Rectum	Bladder	Femur
ECPa	-50	7	7	7
Kw	40	1	1	2
maxEUD ₀	-	EUD ₀ +900	EUD ₀ +900	EUD ₀ +100

OM, optimization method; EUD, equivalent uniform dose; ECPa, equivalent characteristic parameter; PTV, planning target volume.

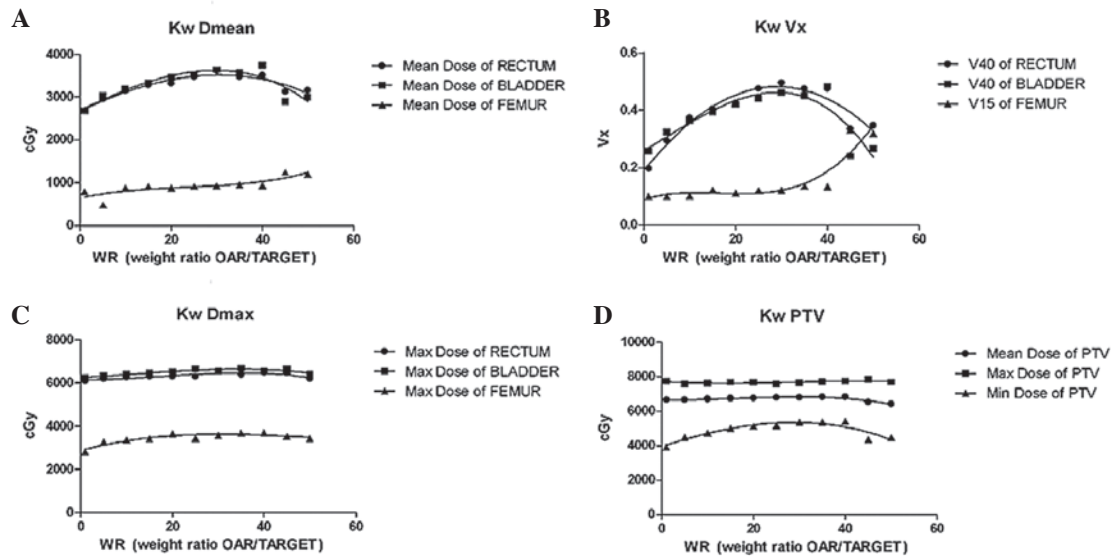


Figure 2. Optimization efficiency of the PTV and OAR dosimetric parameters on the weight 'w' OM. (A) When the OF >1, the weight OM had negative optimization effects on the Vx of the OARs. As the weight of the OARs increased, the irradiated volume of the OARs became bigger. (B) When the OF >1, the Dmean of the rectum and bladder had the same trends as Kw changed. When Kw equaled 40, the Dmean values of the above two OARs were at their peaks. The values then decreased when the Kw continued to increase. (C) When the OF <1, Kw had no significant optimization effects on reducing the Dmax of the OARs. (D) When OF=1, the Dmean and Dmax of the PTV showed similar variation trends. The minimum dose of the PTV firstly increased and then decreased when the weight ratio w increased. OF, optimization factor; OM, optimization method; OAR, organ at risk; Dmean, mean dose; Dmax, maximum dose; Vx, volume dose; PTV, planning target volume.

was adopted by the TPS, which fell into the trap of the local minimum value. These results suggest that the way to more efficiently use ECPa is to reduce the maxDose of the OARS; however, reducing the meanDose or Vx of the OARS has almost no effect.

Optimization efficiency of the PTV and OAR dosimetric parameters of the 'w' OM. To determine the optimization efficiency of the 'w' OM, the meanDose, maxDose and Vx of the OARs were studied when 'w' was changed. Fig. 2 and Table IV show the optimization efficiency of the PTV and OAR dosimetric parameters of the 'w' OM. The results suggest that there was no clear efficiency in using the 'w' OM to optimize the maxDose of the OARs, while there is significant efficiency in optimizing the Vx and meanDose of the OARs.

Optimization efficiency of the PTV and OAR dosimetric parameters on the maxEUD constraint OM. To determine the optimization efficiency of the maxEUD constraint method, the meanDose, maxDose and Vx of the OARs were

studied. Fig. 3 and Table V show the optimization efficiency of the PTV and OAR dosimetric parameters on the maxEUD constraint OM. These results suggest that, compared with the other two methods, maxEUD constraint optimization exhibited the best optimization efficiency, although the optimization results appeared poor when the maxEUD was increased.

A notable selective optimization phenomenon exists in the dose optimization of the target and OAR with ECPa. The increase in 'a' did not work to reduce the Vx of the bladder, rectum and femur, and the resulting OF was <0.01, which indicates a weak valid optimization, so weak it may be considered invalid; however, it had the highest optimization efficiency in decreasing the maxDose point in the OARs when the ECPa was increased. The resulting OF of >1 coincided with our earlier investigation into the usage of ECPa to eliminate the dose hotspots in the OARs. An OF >1 was also useful in lowering the meanDose of the OARs, with the exception of the rectum (where the OF=0.14, as shown in Table III). Table IV indicates that it is useless to utilize

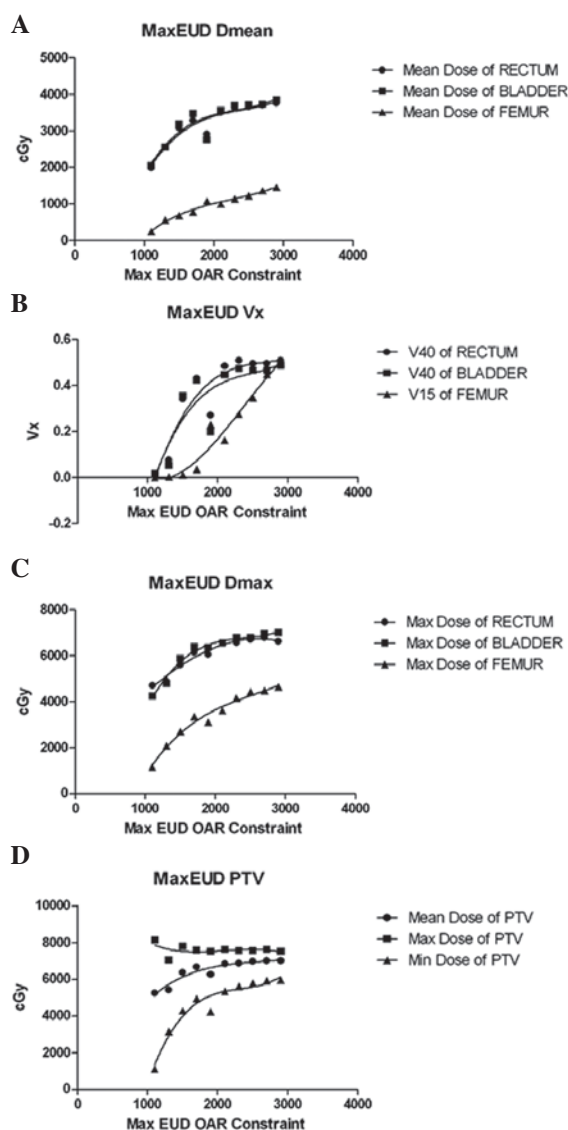


Figure 3. Optimization efficiency of the PTV and OAR dosimetric parameters in the maxEUD constraint OM. No selected optimization phenomenon was observed from the analysis of the OFs in Table V. The biological background constraint max/minEUD OM, which has equilibrium optimization effects on the Dmax, Dmean and Vx, is shown. (A) The maxEUD constraint OM had little optimization effect on the Dmean of the OARs. (B) The maxEUD constraint OM did not reduce the Vx of the OARs. (C) The maxEUD constraint OM did not reduce the Dmax of the OARs. (D) When OF >1 and the dose constraint to the OAR became looser, the dosimetric parameters of the PTV became more satisfactory (the minimum dose became higher and the Dmax was decreased). OM, optimization method; OF, optimization factor; OAR, organ at risk; EUD, equivalent uniform dose; Dmean, mean dose; Dmax, maximum dose; Vx, volume dose; PTV, planning target volume.

the OM 'w' to optimize the maxDose of the OARs, as the OFs for the bladder, rectum and femur were 0.00037, 0.00258 and 0.00396, respectively; however, it did reduce the Vx and meanDose of the OARs (minimum OF, >4). These results suggest that the 'w' OM had a successful effect on Vx and meanDose, but had almost no effect on maxDose.

Finally, the OOS was determined via analysis of the dose-parameter tables based on the CF and OF analysis. The OOS in the Pinnacle V_{7.6} TPS with IMRT function was

Table VII. Mathematical analysis of the optimization logic.

ECPa	Rectum		
	V ₄₀	maxDose	meanDose
OF	0.00365	-37.1	0.140
CF	-0.530	0.906	0.120
MOR	1	7	1

ECPa, equivalent characteristic parameter; OF, optimization factor; CF, correlation coefficient; MOR, most optimum region; maxDose, maximum dose; meanDose, mean dose; V₄₀, percentage of the planning target volume receiving 40% of the prescribed dose.

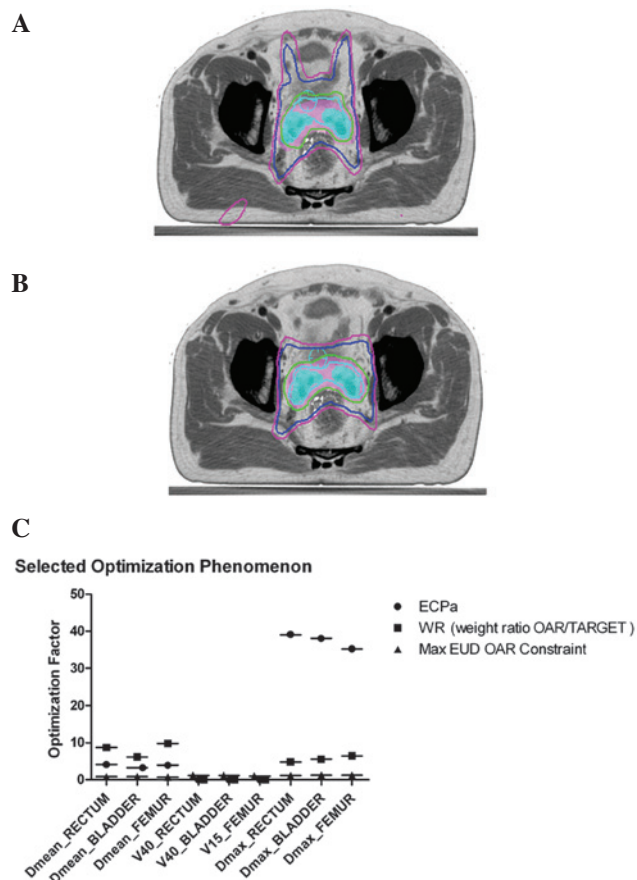


Figure 4. SOP in different OMs. (A) Transection-slice dose map from a plan without OOS. The transverse dose distribution map from one patient with prostate cancer is shown. The light-blue region was defined as gross target volume, and the light-pink region indicated the planning target volume. The isodose line from the inside to the outside was 72 Gy (100% of the prescribed dose). (B) Transection-slice dose map from the same plan as that shown in (A), but with OOS. (C) An SOP existed when different OMs were used to optimize dose distribution to the targets and OARs. SOP, selected optimization phenomenon; OM, optimization method; OOS, overall optimization space; OAR, organ at risk; EUD, equivalent uniform dose; Dmean, mean dose; Dmax, maximum dose; Vx, volume dose; ECPa, equivalent characteristic parameter.

transposed as shown in Table VI, and a dose comparison was performed to evaluate the efficacy of the OOS. The result is shown in Fig. 4.

Discussion

The parameters in the optimization can be considered as a manual, pre-computer-optimized process for the IMRT plan (10). The present study was focused on a quantitative analysis of a manual, pre-computer-optimized process of IMRT planning via a statistically based CF and the optimization efficiency factor analysis theory.

In the demonstrated optimization logic, every optimization was performed so that the most important f_k result was completely satisfied. In this logic, however, there exists an inherited exclusive selection relationship (IESR). The IESR means that the improvement of the PTV-covered dose will make the protection effort of the OARs a sacrifice. In other words, an unavoidable consequence of increased tumor control probability (11) is an increase in normal tissue complication probability (12).

In the present study of the prostate cancer case, the maximum point dose of the rectum and the target dosimetric parameter V_{95} were seen as having the closest association among all the pairs of relevant dosimetric data (Table VII). The resulting CF_{max} was 0.906 (Table III), a value ~ 1.7 - and 7.6-fold higher than the CF values of 0.53 and 0.12, respectively. When an $ECPa=7$ was selected, the target dose parameter V_{95} of the PTV was satisfied; however, it was noted that the optimal value of the meanDose of the rectum was obtained only when $ECPa=1$ was selected, and the corresponding correction factor was 0.53. The CF_{max} was considered, and the relevant $a=7$ was selected as the MOR in this situation. The marked decreasing efforts in the irradiation volume of the rectum ($a=7$ to $a=1$) is likely to conversely affect the satisfaction of the target volume V_{95} in ~ 0.5 CF. If the OF is a useful optimization (OF >0.5), the above-proposed situation must be considered by adjusting the selection of the optimization parameters for the optimal value. Furthermore, an amended selection of the MOR may be more necessary. Although the corrected MOR (4.93) was different from the pre-amended value (7.00), the effect of the final dose in the OARs and the target was slightly diminished. This may make our statistical analysis theory more adoptable.

The analytical model for the selection of OOS based on statistical analysis methods has both theoretical and clinical significance.

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