



Research Article

Feasibility of Multisolutions Optimization Technique for Real-Time HDR Brachytherapy of Prostate

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The purpose of this study was to evaluate the efficacy of multisolutions optimization algorithm for High Dose Rate (HDR) brachytherapy of prostate. In this retrospective study, we included data from 20 prostate cancer patients who underwent ultrasound based real time HDR Brachytherapy at institution. The treatment plans of all 20 patients were optimized in Oncentra Prostate treatment planning system (TPS) using inverse dose volume histogram based optimization followed by graphical optimization (GRO) in real time. The data of all the patients were retrieved later, and the treatment plans were re-optimized using multisolutions dose volume histogram based optimization (MDVHO) and multisolutions variance based optimization (MVBO) algorithms with same set of dose constraints, same number of catheters, and same contour set as in GRO. Several Pareto optimal solutions were obtained by varying the weighting factors of composite objective function in finite steps of adequate resolutions. These solutions were then stored in the database of TPS and same decision criteria was employed to pick the final solution using a decision engine. The average values for planning target volume receiving 100% of prescribed dose (V100) for MDVHO, MVBO, and GRO were 95.03%, 86.72% and 97.56%, respectively. The average V100 due to MDVHO was statistically significant ($P = 0.002$) in comparison to MVBO, whereas the average V100 due to MDVHO and GRO was not statistically significant ($P = 0.066$). In conclusion, the MDVHO can provide comparable solutions to typical clinical optimizations using GRO within clinically reasonable amount of time. In most of the cases, the plans created by MVBO were not clinically acceptable without users' further manual intervention.

Keywords: High Dose Rate; Brachytherapy; Optimization; Pareto optimal; Multisolutions; Treatment Planning System**Peer Reviewer:** Xue Gong, MD, PhD, Department of Microbiology and Immunology, Stanford University, United States.**Received:** April 21, 2013; **Accepted:** July 12, 2013; **Published:** August 20, 2013**Competing Interests:** The authors have declared that no competing interests exist.**Copyright:** 2013 Shyam Pokharel *et al.* This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.***Correspondence to:** Shyam Pokharel, Dept. of Medical Physics, Premiere Oncology, Florida, USA.

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Introduction

The quality of computer optimized treatment plan is

primarily determined by the choice of an objective function, constraints, and optimization algorithm. The primary objective of radiation therapy, i.e., to deliver

the curative dose to the target while sparing neighboring critical structures can now be achieved with high degree of accuracy due to technological advancement [1]. Furthermore, the rapid improvement in three dimensional (3D) imaging modalities coupled with advancement in computer technology has now made possible to create truly anatomy based inverse optimization [2, 3]. However, radiation therapy optimization is inherently multiobjective problem often with competing objectives. For example, in case of prostate cancer, we need to have sufficient planning target volume (PTV) coverage while sparing the organs at risk (OARs) such as urethra, bladder, and rectum. However, while increasing the dose to the PTV, it also results in increased dose outside the PTV, thus increasing radiation exposure to the OARs. These objectives cannot be optimized to their best simultaneously and a trade-off among the objectives exists [4, 5].

It is becoming clear that, there is no single best solution rather there are many best compromises so called Pareto optimal or efficient solutions [6, 7]. A Pareto optimal solution is the one which cannot be improved in one objective without worsening at least one of the other objectives. The line joining the Pareto optimal solutions is called Pareto front or Pareto limit and shows where best compromise between the objectives can be achieved with the variation of their relative importance. [6] Figure 1 shows the Pareto optimal solutions for a simplified case of two objectives, $f_1(x)$ and $f_2(x)$. In Figure 1, solutions 1 and 3 are non-dominated Pareto optimal solutions. Solution 1 has a smaller f_1 value $f_1(1)$ than the value $f_1(3)$ of solution 3 but $f_2(1)$ of solution 1 is bigger than $f_2(3)$ of solution 3. Solution 1 has both objectives smaller than solution 2 simultaneously. Therefore, solution 2 is not Pareto optimal. The aim of multiobjective optimization is to find a representative set of non-dominated solutions.

Several investigators have studied multiobjective optimization for both external beam radiation therapy (EBRT) and brachytherapy with different optimization strategies [6-18]. For example, Milickovic *et al.* [6] studied the multiobjective anatomy based dose optimization for high dose rate (HDR) brachytherapy with constraints free deterministic algorithms. Schreibmann *et al.* [9] proposed a hybrid multiobjective evolutionary

optimization algorithm for intensity-modulated radiotherapy inverse planning. Craft *et al.* [14], used convex multicriteria dose optimization to make the planning of volumetric modulated arc therapy faster and explored the tradeoffs between planning objectives and delivery efficiency. In the recent study by Giantsoudi *et al.*, [15] authors studied the feasibility of a new inverse planning technique based on the generalized equivalent uniform dose for image-guided HDR prostate cancer brachytherapy in comparison to conventional dose-volume based optimization. In another study by Pardo-Montero [16] *et al.*, an approach to multiobjective optimization of rotational therapy treatments was investigated.

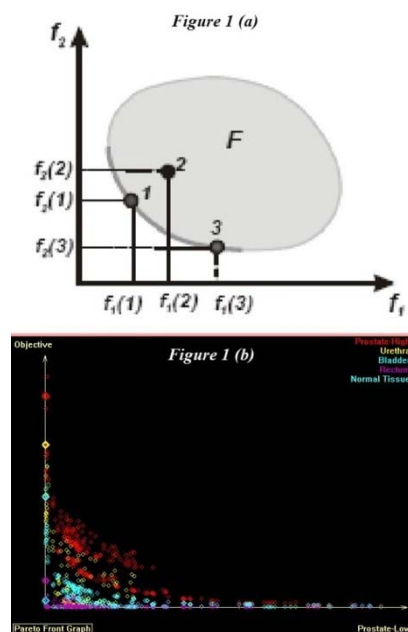


Figure 1 Pareto front graph: (a) Example of bi-objective space (f_1, f_2) and (b) Pareto front graph of DVH based multi-objective optimization (MDVHO). Solutions 1 and 3 (a) are non-dominated Pareto optimal solutions. Solution 1 has a smaller f_1 value $f_1(1)$ than the value $f_1(3)$ of solution 3 but $f_2(1)$ of solution 1 is bigger than $f_2(3)$ of solution 3. Solution 1 has both objectives smaller than solution 2 simultaneously. Therefore solution 2 is not Pareto optimal. The aim of multiobjective optimization is to find the representative set of non-dominated solutions.

However, to the best of our knowledge, the multiobjective optimization techniques along with clinically relevant strategy for HDR brachytherapy of prostate remain to be addressed, especially with focus on real-time intra-operative procedures. For real-time procedures, the algorithm should be fast enough to produce a clinically optimal plan within a reasonable amount of

time, preferably in less than five minutes. Although deterministic algorithms are fast, the final result depends on the initial starting point and can be trapped in the local minima if such minima are in the objective function [18]. It has been reported that multiple local minima may occur in radiotherapy optimization problems with dose volume constraints [18]. To overcome this issue, the planner has to run the optimization several times with different starting points. Stochastic algorithms, such as simulated annealing (SA) or genetic algorithm (GA) are slow but can escape from local minima and will converge to a global minimum if allowed to execute for a sufficient amount of time [10]. The problem with these algorithms is the significant amount of time they require to optimize, which may not be achievable in real clinical environment.

For instance, the graphical optimization (GRO) is a manual optimization technique [12], and the quality of final plan heavily depends on the experience and expertise of the planner. This optimization technique is most commonly used by the clinicians including at our institution. Since GRO is a manual technique, it takes significant amount of time to achieve a clinically acceptable plan, and such long process may not particularly desirable in real time procedures. The purpose of this study is to investigate an alternative technique which is robust, fast and can create comparable if not better plans than the plans created manually by an experienced brachytherapy team without further manual intervention. The algorithms chosen for the present study are multisolutions dose volume histogram based optimization (MDVHO) and multisolutions variance based optimization (MBVO). The DVH and variance based objective functions have been chosen to study the quality of plans with the choice of objective function. Additionally, both the MDVHO and MBVO are gradient based fast deterministic algorithms, which can create several hundred plans in few minutes time.

Materials and Methods

This is a retrospective study consisting of data from 20 patients who underwent ultrasound based real time HDR Brachytherapy of the prostate at institution. The clinical treatment plans were all carried out intraoperatively with real-time live ultrasound images and real-time dynamic dosimetry using treatment planning system (TPS) called Oncentra Prostate (SWIFT, version 3.0) by Nucletron [12]. The TPS is dedicated to ultrasound based real-time HDR

brachytherapy of the prostate. The TPS is equipped with several classes of optimization algorithms, ranging from manual adjustment of dwell times to multiobjective evolutionary inverse optimization. Catheters were implanted with the guidance of transrectal ultrasound (TRUS) based on the clinical experience, and post implant optimization was carried out with inverse DVHO utilizing default importance factors stored in the TPS. The default importance factors were determined for first clinical case with a trial and error approach and then defaulted in the TPS. Most of the times, the plans were not clinically acceptable and further improvement of plans was performed using GRO. The isodose lines in GRO are manipulated slice by slice and the TPS adjusts the dwell times accordingly. Manipulation of isodose line in particular slice may adversely affect to the neighboring slices and the process goes on till planner comes up with acceptable plan. This is a tedious process and may take significant amount of time which is particularly undesirable in real time procedures. The data from the original treatment plans were retrieved and the treatment plans were re-optimized using MDVHO and multiobjective MVBO algorithms under identical conditions.

Multiobjective dose volume histogram based optimization

The MDVHO algorithm is an anatomy based inverse optimization using gradient based fast deterministic algorithm [12]. Its goal is to create an ideal DVH based on user defined dose and dose volume limits to different structures and moves straight downhill iteratively based on user defined convergence setting [12]. For multiobjective optimization technique, it requires the planner to have some prior knowledge of relative weights and their influence in the final result [12]. However, in general, this is not possible for the planner to have prior knowledge of set of importance factors that map from important space to optimization space with desirable dosimetric results. Even if the solution obtained for particular set of importance factors is global optimum, using other set of importance factors, other better results can be obtained. This often requires the repetition of optimization algorithm several times with different set of importance factors till the planner feels that the optimized plan is clinically acceptable in trial and

error fashion. If the planner finds some of the objectives not satisfactory, then he/she increases the corresponding weight to make it acceptable. Often, this has the deteriorating effect in other objectives and the process can be very tedious especially if one is dealing with several objectives. To get around this issue, we have adopted different optimization approach in this study. In this approach, we define the range of importance factors for each objective considered instead of single fixed set of importance factors.

Dose limits and range of importance factors used for different objectives in this study are DL, PTV = (100% of PD and range, 0.1 -1.0), DH, PTV = (150% of PD and range, 0.001- 1.0), DH, URETHRA = (120% of PD and range, 0.001-1.0), DH, RECTUM =(85 % of PD and range, 0.001-1.0), DH, BLADDER = (85% of PD and range, 0.001-1.0), and DH, NORMAL TISSUE = (120% of PD and range, 0.001-1.0) respectively. Based on user defined number of steps per objective, the optimization algorithm finds several solutions with different combinations of importance factors and stores them in the database of TPS. The planner has to choose one of the solutions that best meet the clinical goals from the pool of these solutions. The range of importance factors chosen for the prostate low (conformity objective) is 0.1 to 1.0. This is for the purpose of scanning the subset of Pareto front which is clinically relevant. This means, we do not want the solution at the extreme end of Pareto front where conformity is very low.

Multiobjective variance based optimization algorithm

The concept of MVBO is exactly same as the MDVHO as explained before with the only difference in the form of objective function used [12]. The MVBO is based on variance based objective and its goal is to minimize variance between dose at the sampling point and mean dose on the region of interest (ROI) chosen. The range of importance factors and dose limits chosen for MVBO algorithm are exactly same as in MDVHO algorithm. The conformity and homogeneity objectives in MVBO algorithm correspond to PTV low and PTV high objectives in MDVHO algorithm. For details on the optimization strategies employed for both MDVHO

and MVBO, readers are advised to refer to Baltas *et al.* [12].

Execution of optimization algorithms

Both MDVHO and MVBO are deterministic algorithms which move straight downhill in the search space and converge at nearby minima [12]. The difference between these two optimization algorithms is the form of objective function penalization mechanism. The penalization in MVBO is quadratic when the dose is outside the acceptable limit as opposed to linear in MDVHO [12].

In either of the multiobjective optimization algorithms considered in this study, the algorithm runs several times with different set of importance factors based on user defined range of importance factors with finite increments for several objectives considered in composite objective function. Several Pareto optimal solutions are stored in the database of TPS forming the pool of alternative solutions. The Pareto front graph for several objectives after the completion of optimization is as shown in Figure1(a). In Figure 1 (b), several objectives are plotted against the objective of prostate low thereby reducing multidimensional polyhedron into simple two dimensional plots. From the pool of these solutions, one with best dosimetric distribution is to be selected by the planner. The planner can select the final solution using decision engine as per the requirement of clinical needs.

Dosimetric evaluation

Isodose distribution and several dosimetric quality indexes obtained from cumulative DVH were used for the evaluation and qualitative and quantitative comparison of different treatment plans optimized by GRO, MDVHO, and MVBO. The following are the dosimetric indices calculated to compare the treatment plans quantitatively.

1. D90: the dose that covers 90% of PTV
2. V100, V150 and V200: the volume of PTV receiving 100%, 150% and 200% of the PD, respectively.
3. D10 and Dmeanof OARs: D10 is the minimum dose to 10 % of the OAR volume

(urethra, bladder or rectum). Dmean is the mean dose to a given volume of an OAR.

4. Homogeneity Index (HI) [19]: defined as $HI = (V100 - V150)/V100$. This index is used to assess the volume of hot spot generated relative to the treatment volume [19].
5. Conformal Index (COIN) [20]: a unique quality index that describes how well the reference isodose covers the target volume and excludes non-target volumes. It is defined as $COIN = (PTV_{ref}/PTV) \times (PTV_{ref}/V_{ref})$, where PTV_{ref} is the volume of PTV that receives dose equal to or greater than PD. V_{ref} is the volume receiving the PD [19]. The ideal situation is that in which COIN is equal to 1. In real clinical situations it is always less than 1, and if all other parameters are comparable then a treatment plan with higher COIN should be favored.

Selection criteria for the final solution

Decision engine in the treatment planning system was used to select the final solution in case of both MDVHO and MVBO [12]. The decision engine has all the user defined evaluation/ decision dosimetric parameters obtainable from cumulative DVH for both PTV and OARs. The decision engine filter out only those solutions which satisfy the user defined dosimetric criteria in the evaluation/ decision protocol. The same dosimetric criteria were used to select the final solution in case of both MDVHO and MVBO. We first filtered only those solutions with D90 for PTV from 100% to 115% of the prescription dose (PD). Then from the remaining solutions, we filtered only those solutions with PTV V100 \geq 95% of the PD. It was followed by constraining solutions with PTV V150 \leq 30% of the PD. Then from the left over solutions, we chose the one with highest COIN. We followed this strategy in sequence to select the final solution in this study. Figure 2 shows DVHs corresponding to several potential solutions left after many others got filtered out by decision engine for not fulfilling the dosimetric criteria set by the planner. However, MVBO resulted most of the solutions in most of the cases with D90 and V100 less than the above mentioned limits. Under this condition dosimetric requirements were decreased in steps of

2% for D90 and V100 and increased in steps of 2% for V150. The final solution among the left over was selected with COIN as before.

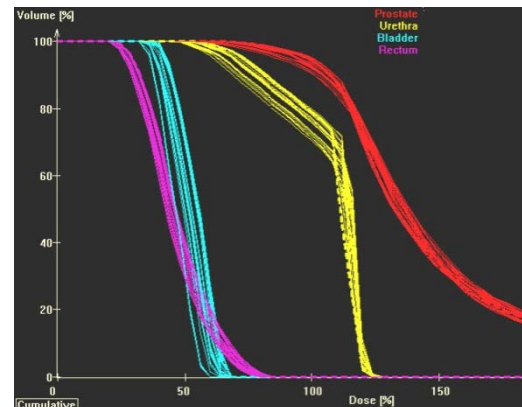


Figure 2 Dose-volume Histograms (DVHs) corresponding to several potential solutions due to DVH based multi-objective optimization (MDVHO). Several others got filtered out by a decision engine for not fulfilling the dosimetric criteria set by the planner. The final solution can be selected among these solutions either selecting the DVH graphically which best fulfills the clinical goals or by forcing the decision engine to single out the solution by stringent dosimetric requirements.

Statistical analysis

Paired Student's t-test at 5 % level of significance was used to make statistical comparison of different dosimetric quality indices of treatment plans optimized by different optimization algorithms. The statistical analysis was carried out using Microsoft Excel. The statistical comparisons were carried out between MDVHO vs. MDVO, and MDVHO vs. GRO.

Results

The average number of catheters implanted was 14 (range, 11-17) and the average clinical target volume (CTV) was 43.27cc (range, 12.50 -67.56 cc), which in our case served as the PTV as well. The average time taken to perform MDVHO and MVBO optimization with about 260 solutions were 5.6 minutes (range, 3-9 minutes) and 1.9 minutes (range, 1-3 minutes), respectively. The average time taken for optimization using GRO for clinical plans was 25 minutes (range, 20-35 minutes). In MDVHO and

MVBO optimizations, the number of dose sampling points for prostate was 500 and number of dose sampling points for all other structures considered in optimization such as urethra, bladder, rectum and normal tissue were 300 each. This sampling was used only for the optimization processes. For an evaluation purpose, we increased sampling points for each of the objectives to 1000. The above sampling strategy was employed to reduce the overall calculation time without compromising the final dose calculation accuracy. Most of the pareto optimal plans get filtered out for not fulfilling the clinical objectives. The goal was to reduce the time spent on those solutions. The goal was to reduce the time spent on those solutions. Most of the treatment planning systems uses coarse calculation (either reducing the sampling points or approximating the dose calculation or both) in optimization and increase the dose calculation accuracy in final dose calculation to speed up the overall calculation time. The end result is slightly different DVH in final calculation than in optimization stage. Once the optimized plans meet the clinical objectives, the dose calculation accuracy has to be increased for final evaluation. The above sampling strategy removes unwanted solutions quickly without compromising final dose calculation accuracy for clinically relevant plans. The above sampling strategy neither changes result nor

conclusion.

Figure 3 shows the isodose distribution of the same axial slice of a particular patient with plan optimized by (a) MDVHO, (b) MVBO, and (c) GRO, respectively. From isodose distribution, it can be observed that all three optimization algorithms have resulted adequate PTV coverage with MVBO being most conformal and highly inhomogeneous for this particular reference slice. Most of the MVBO optimized plans in this study have resulted adequate coverage with high conformity in central slices and lacked adequate coverage to the slices towards base and apex of the prostate. This is due to the variance reduction in MVBO in which any dose outside the acceptable range gets penalized quadratically. Similarly, Figure 4 (a) shows the cumulative DVH comparison between treatment plans optimized by MDVHO and MVBO of the same patient with same range of importance factors, dosimetric constraints and selection strategy for the final solution. From the DVH comparison, it appears that MDVHO algorithm has produced higher V100 (96.89% vs. 86.18% of PD) with smaller V150 (33.44% vs. 42.18% of PD) with clinically acceptable doses to the OARs. Figure 4 (b) shows that MDVHO has resulted smaller bladder dose with comparable dose to prostate, urethra, and rectum in comparison to GRO.

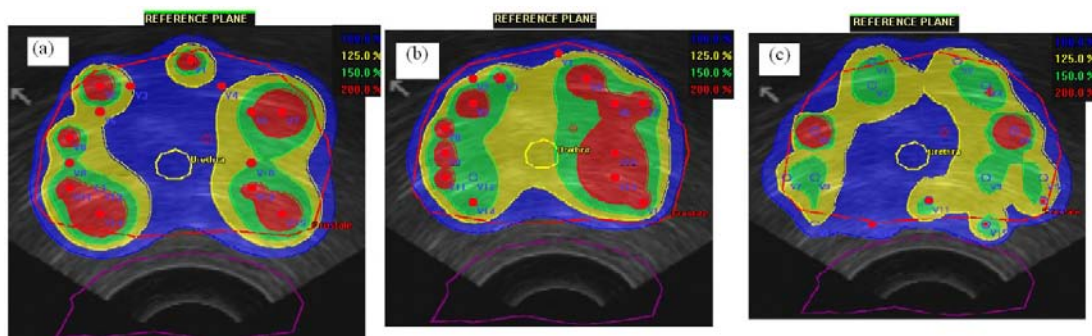


Figure 3 Isodose distribution in color-wash form with treatment plan optimization algorithms (a) MDVHO, (b) MVBO, and (c) GRO for the same axial slice. The planning target volume (PTV) is enclosed with red contour and blue = 100% isodose, yellow = 125% isodose, green = 150% isodose, red = 200% isodose.

Abbreviations: MDVHO = dose volume histogram based multiobjective optimization, MVBO = multiobjective variance based optimization, GRO = graphical optimization.

The statistical analysis of dosimetric quality indices for both PTV and OARs is presented in Tables 1 and 2, respectively. The results are averaged over 20 analyzed patients. The average D_{90} (106.42 Gy vs. 93.33 Gy) was statistically higher ($P = 0.002$) with MDVHO in comparison to MVBO.

However, the average D_{90} (106.42 Gy vs. 110.88 Gy) was statistically lower ($P = 0.015$) with MDVHO in comparison to GRO. This signifies that inverse anatomy based MDVHO algorithm can create more homogeneous plan than the manual GRO algorithm for similar target coverage. The average V_{100} (95.05%

vs.86.72%) for MDVHO was statistically higher ($P=0.002$) in comparison to MVBO. This suggests that even though MBVO can create highly conformal plans due to the dominance of variance reduction, it

lacks an adequate target coverage to be clinically acceptable. In contrast, the average V_{100} (95.03 vs. 97.56) was not statistically significant ($P = 0.066$) with MDVHO in comparison to GRO.

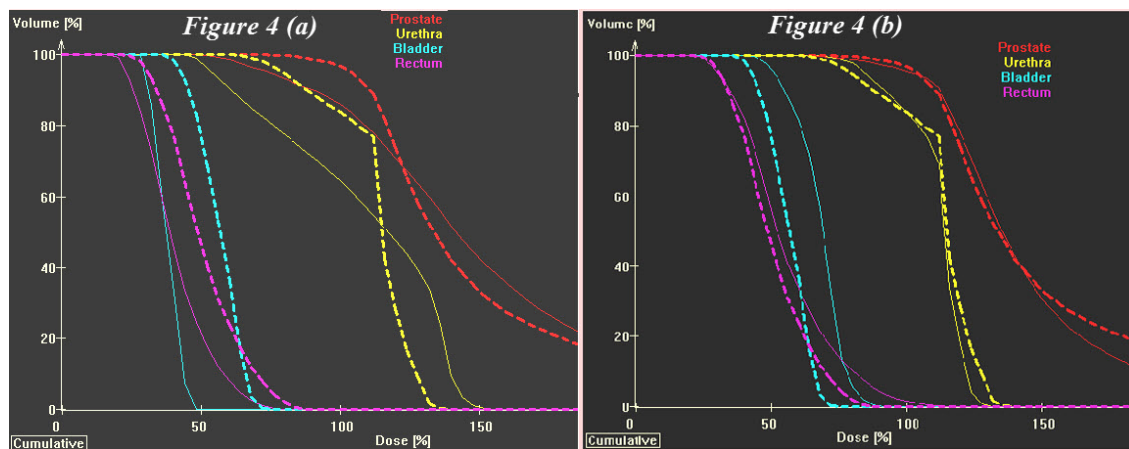


Figure 4 Dose-volume histogram (DVH) comparison between: (a) MDVHO (broken lines) and MVBO (solid lines). MDVHO based optimization resulted in higher V_{100} together with significant reduction in V_{150} compared to MVBO optimization. (b) MDVHO (broken lines) and GRO (solid lines). MDVHO resulted smaller bladder dose with comparable dose to prostate, urethra and rectum compared to GRO. **Abbreviations:** MDVHO = DVH based multiobjective optimization, MVBO = multiobjective variance based optimization, GRO = graphical optimization

Table 1 Dosimetric indices for the PTV with different optimization algorithms.

Optimization algorithm	D10 (Urethra)	Dmean (Urethra)	D10 (Bladder)	Dmean (Bladder)	D10 (Rectum)	Dmean (Rectum)
GRO						
Average	127.09	113.47	76.47	55.80	69.40	48.99
Median	123.84	112.14	69.92	55.85	69.02	47.57
σ	13.54	8.05	20.26	14.53	8.77	7.03
Minimum	117.01	101.98	51.18	36.17	50.32	36.52
Maximum	181.94	141.84	118.96	87.66	85.66	62.18
MDVHO						
Average	130.01	114.89	71.06	58.18	68.95	48.87
Median	124.66	112.20	64.13	56.61	67.80	48.62
σ	17.69	13.20	31.07	18.75	8.39	6.96
Minimum	109.35	97.89	38.19	32.70	53.24	36.52
Maximum	166.03	153.70	181.95	112.06	92.72	66.17
P-value	0.56	0.40	0.45	0.56	0.810	0.935
MVBO						
Average	131.35	107.39	53.79	39.84	61.21	42.10
Median	131.65	110.74	51.11	37.98	61.79	42.49
σ	15.10	11.33	11.95	9.42	9.25	6.95
Minimum	102.09	83.16	37.67	26.36	46.37	30.54
Maximum	162.04	123.14	72.40	55.96	82.41	56.29
p-value	0.756	0.04	0.01	0.0004	<0.001	<0.001

Abbreviations: MDVHO = dose volume histogram based multiobjective optimization, MVBO = multiobjective variance based optimization, GRO = graphical optimization. PTV = planning target volume; PD = prescription dose; σ = standard deviation; COIN = conformal index; HI = homogeneity index; D_{90} = minimum dose to 90% of PTV; V_{100} , V_{150} and V_{200} = PTV receiving 100%, 150% and 200% of prescription dose respectively. (The values are averaged over 20 analyzed patients)

Table 2 Dose (Gy) to the OARs with different optimization algorithms.

Optimization algorithm	D90 (Gy) (% PD)	V100 (%) (% PTV)	V150 (%) (% PTV)	V200 (%) (% PTV)	COIN	HI
GRO						
Average	110.88	97.56	31.94	10.46	0.50	0.67
Median	112.18	97.73	30.78	10.44	0.50	0.68
σ	4.85	1.77	7.31	2.69	0.18	0.07
Minimum	102.43	94.04	19.87	6.26	0.19	0.48
Maximum	119.50	99.72	50.10	17.50	0.81	0.79
MDVHO						
Average	106.42	95.03	23.87	8.169	0.65	0.75
Median	107.52	96.77	22.97	7.17	0.64	0.76
σ	5.63	5.73	8.01	3.73	0.06	0.08
Minimum	91.69	76.17	10.80	2.83	0.49	0.56
Maximum	113.77	99.11	43.36	16.59	0.76	0.89
P-value	0.015	0.066	0.007	0.059	0.002	0.011
MVBO						
Average	96.33	86.72	35.61	13.68	0.76	0.59
Median	96.28	87.15	37.76	13.76	0.77	0.59
σ	8.90	6.49	8.41	4.68	0.09	0.08
Minimum	81.05	72.83	15.17	4.93	0.61	0.43
Maximum	114.46	97.38	55.17	25.69	0.92	0.79
P-value	0.002	0.002	<0.001	<0.001	<0.001	<0.001

Abbreviations: MDVHO = dose volume histogram based multiobjective optimization, MVBO = multiobjective variance based optimization, GRO = graphical optimization. D10 = minimum dose to 10% of urethra (or bladder or rectum) volume. Dmean = mean dose to given volume of interest, here urethra, bladder and rectum; σ = standard deviation. (The values are averaged over 20 analyzed patients)

The D_{90} and V_{100} comparisons in the form of box plots are presented in Figure 5. The average V_{150} (23.87% vs. 35.61%) and average V_{200} (8.16% vs. 13.68%) were both statistically lower ($P < 0.001$) with MDVHO in comparison to MVBO (Table 1 and Figure 6). The average V_{150} (23.87% vs. 31.94%) and average V_{200} (8.16% vs. 10.46%) were both statistically lower with MDVHO in comparison to GRO (Table 1 and Figure 6). The average homogeneity index (0.75 vs. 0.59) was statistically higher ($P < 0.001$) with MDVHO in comparison to MVBO (Table 2 and Figure 7). However, average

conformal index (0.65 vs. 0.76) was statistically lower ($P < 0.001$) with MDVHO in comparison to MVBO. The COIN and HI both were statistically higher with MDVHO in comparison to GRO (Table 2 and Figure 7). The average D_{mean} to urethra (114.89 Gy vs. 107.39 Gy) was slightly higher statistically ($P = 0.04$) with MDVHO in comparison to MVBO. However, the minimum dose to 10% volume (D_{10}) of urethra, (130.01 Gy vs. 131.35 Gy) was essentially same ($P = 0.756$) with both MDVHO and MVBO (Table 2 and Figure 8).

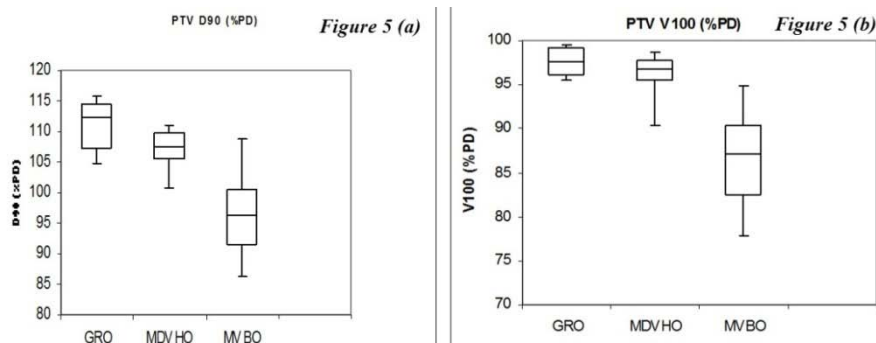


Figure 5 Box and whisker plots of the PTV D_{90} (a) and V_{100} (b) for the four optimization algorithms covered in this study. MVBO has the widest range of D_{90} and V_{100} rendering clinically unacceptable most of the time. The plots present the 10th percentile, 25th percentile, median, 75th percentile and 90th percentile of data used.

Abbreviations: MVBO = multiobjective variance based optimization.

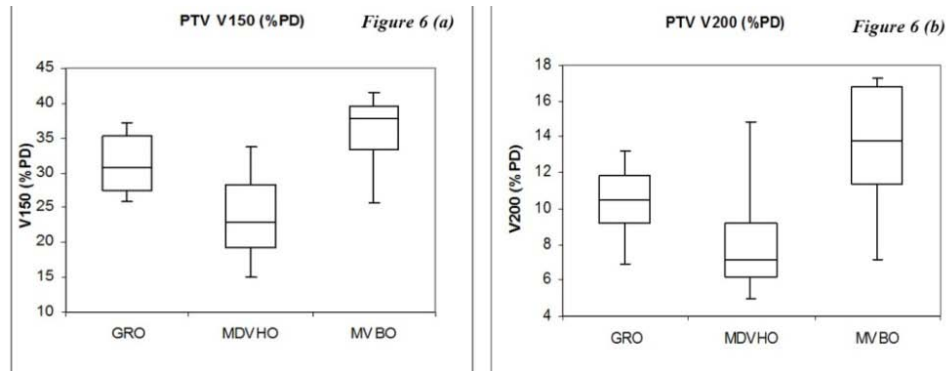


Figure 6 Box plots for V150 and V200 for MDVHO, MVBO and GRO: (a) V150 comparison and (b) V200 comparison. Average V150 (a) and V200 (b) are both significantly smaller with MDVHO compared to both MVBO and GRO. **Abbreviations:** MDVHO = dose volume histogram based multiobjective optimization, MVBO = multiobjective variance based optimization, GRO = graphical optimization

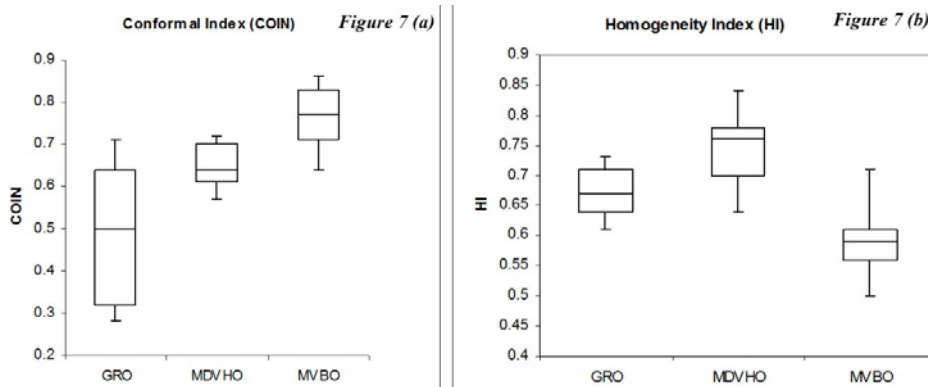


Figure 7 COIN and HI for MDVHO, MVBO and GRO: (a) COIN comparison and (b) HI comparison. GRO has significantly lower COIN (a) compared to both MDVHO and MVBO and HI (b) somewhere in between MDVHO and MVBO. **Abbreviations:** MDVHO = dose volume histogram based multiobjective optimization, MVBO = multiobjective variance based optimization, GRO = graphical optimization, COIN = conformity index, HI = homogeneity index.

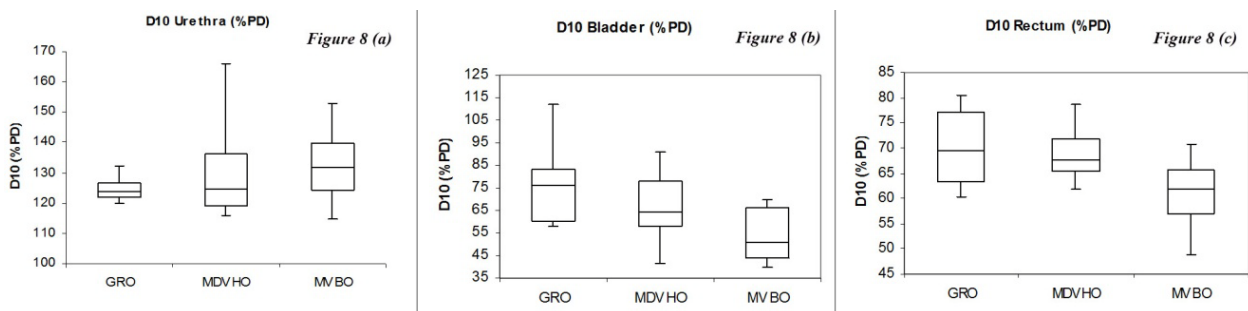


Figure 8 D₁₀ for critical structures for MDVHO, MVBO and GRO: (a) Urethra, (b) Bladder and (c) Rectum. **Abbreviations:** MDVHO = dose volume histogram based multiobjective optimization, MVBO = multiobjective variance based optimization, GRO = graphical optimization

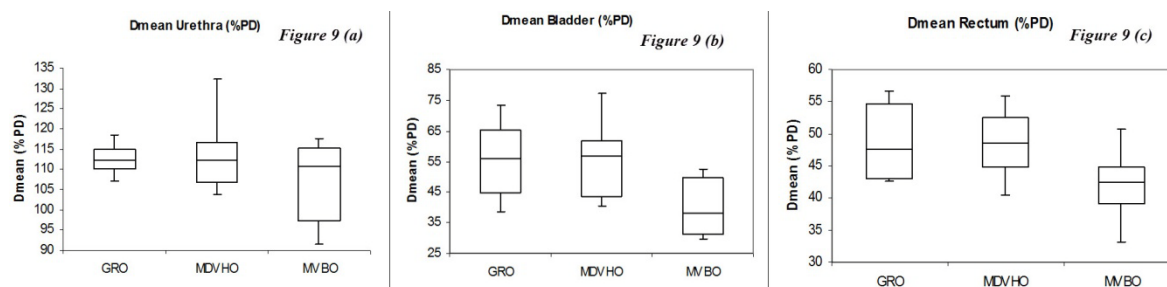


Figure 9 Mean Dose for critical structures for MDVHO, MVBO and GRO: (a) Urethra, (b) Bladder and (c) Rectum.

Abbreviations: MDVHO = dose volume histogram based multiobjective optimization, MVBO = multiobjective variance based optimization, GRO = graphical optimization

The D10 and Dmean for both rectum and bladder were statistically higher with MDVHO in comparison to MVBO (Table 2, Figures 8 and 9). This is again due to highly conformal but the inhomogeneous plans created by MDVO. No statistically significant difference was observed in case of OARs dosimetry in between MDVHO and GRO (Table 2). The box plots for GRO algorithm are included for visual comparison to show the capability of the optimization algorithms in producing a clinically acceptable plan without user's further intervention.

Discussion

There are mainly two critical points unanswered when we use a composite objective function expressed as a weighted sum. First, how can a user know the most appropriate values for the penalties/importance factors? Second, are the penalization values independent of individual anatomy of the patient? In fact, it is not possible to answer both of these queries for any implant and for any patient prior to the execution of optimization itself. The only way to sort out above mentioned queries is to investigate the Pareto front by making several runs of optimization algorithm for given aggregate objective with different sets of importance factors. To get around these issues, we adopted a new optimization strategy in this study. In this strategy, several efficient solutions were created and stored in the database of TPS using both DVH and variance based objectives. The subset of Pareto front which is of clinical interest was only scanned with finite resolutions between two solutions. This is because all Pareto optimal plans are

not of clinical interest such as the one in the extreme end of Pareto front with very low PTV conformity. Even within this subset, there may be infinite number of solutions as the dose distributions continuously change with the change in importance factors and difference between two Pareto optimal plans can become infinitesimal small. This is the reason we changed the importance factors of composite objective function in steps with sufficient resolution such that two plans stored in the database become distinct dosimetrically as well as visually in DVHs and isodose distribution. The final solution was chosen from the pool of solution using the decision engine with the dosimetric constraints as mentioned before.

The quality of optimized treatment plan depends on the objective function, constraints, free variables and the algorithm used to optimize the plan. The MDVHO and MVBO considered in this study are both deterministic algorithms and can converge only to the convex part of the objective space. To make fair comparison, no manual adjustments of any forms were performed. The MDVHO and MVBO plans were optimized under exactly identical conditions and selection of final solution was subjected to same dosimetric constraints. In case of MDVHO algorithm, the final solution selected under the aforementioned conditions, resulted clinically acceptable dosimetric indices in nearly all of the cases in this study. Clinically acceptable plans include PTV coverage of at least 90% PD while meeting non-target tissue constraints. In fact, 18 out of 20 cases studied were clinically acceptable without user further intervention to improve the plan manually.

However, some extreme cases in which the pool of solutions with highest V_{100} for the PTV as low as 76.17 % of PD were also observed. This is probably due to the deterministic nature of the algorithm in which all the solutions get converged in the convex part of the solution space.

However, even with the scanning of clinically most relevant part of Pareto front in this study, V_{100} for PTV in most of the cases due to MVBO algorithm resulted, the pool of solutions with less than 90% of the prescription dose. The solutions with V_{100} for PTV with less than 90% of the prescription dose are, in general, not acceptable clinically. In fact, only 6 out of 20 cases met clinical acceptable criteria with MVBO. Due to the dominance of conformity objective f_s on the surface of PTV, the higher value of V_{100} achievable is limited even with the maximum value of importance factor assigned to it. This signifies the importance of the form of objective function and penalty mechanisms in particular application in optimization algorithm. The objective function must capture the essence of clinical goals in order to produce the desired results for particular application. It is however possible that, the form of objective function efficient for particular application under particular conditions may not be equally efficient in other form of applications. So, most of the MVBO plans in this study under the stated conditions need further user's intervention to make them clinically acceptable. These results signify that scanning pareto front is of little help if we do not have a suitable form of objective function. Even if we have a suitable form of objective function for a particular application, scanning clinically relevant part of pareto front does not always give us clinically acceptable plans. This is probably due to the convergence of all the solutions in the convex part of objective function for a given dose and dose volume constraints. This means all the solutions got converged in local minimum in solution space. This agrees with deterministic nature of the algorithm. Probably due to this reason, two cases did not meet clinically acceptability criteria without user further intervention optimized with MDVHO.

Conclusion

The MDVHO algorithm can create a spectrum of alternative solutions and the final solution chosen from the spectrum using the decision engine is clinically acceptable in most of the cases without planner's further interventions. In addition, the MDVHO can provide comparable solutions to typical clinical optimizations with GRO within a clinically reasonable amount of time regardless of planner's experience and expertise. MDVHO algorithm is appealing in real time intraoperative procedures as it can create clinically acceptable plans in fraction of time to that of GRO independent of planner experience and expertise. The MVBO can create a spectrum of solutions that are highly conformal but the upper limit of dosimetric parameter such as V_{100} is limited by the dominance of the variance reduction objective on the surface (i.e., conformity objective even if we scan the clinically relevant part of Pareto front). Most of the plans optimized by MVBO algorithm did not meet the clinical acceptable criteria. Thus, scanning even clinically relevant Pareto front is of little help, if we do not have the suitable form of objective function in real clinical applications.

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