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Effective Use of Generalized Equivalent Uniform Dose-Based Optimization on Dose-Volume Objectives in Volumetric Modulated Arc (VMAT) Radiation Therapy for Prostate Cancer

Patnaikuni SK, Jain RR, Saini SM[1], Chandola RM, Azad SK, Back M, Sinha A[2]& Choudhary V.

Department of Radiotherapy, Pt JNM Medical College, Regional Cancer Center, Raipur (C.G)
[1]Department of Physics, National Institute of Technology (NIT), Raipur (C.G.)
[2]Department of Mathematics, National Institute of Technology (NIT), Raipur (C.G.)
Corresponding Author: Dr.R R Jain, Assistant Professor, Radiotherapy, Regional Cancer Center, Raipur (C.G)

***Abstract**: High Energy Radiation causes most damage to the rapidly dividing cells, therefore it is useful in treatment of cancer because tumor cells divide extreme rapidly. (Several mechanisms can be used to deliver radiations to tumor by modern treatment planning systems on the basis of radiation dose planning). The goal of radiation therapy is to deliver a therapeutic radiation dose to target tissue organs while minimizing the risk of normal tissue complications by evaluating biological based 3D treatment planning. The purpose of present work is to study the effective use of equivalent uniform dose (EUD) based optimization in volumetric modulated arc radiation treatment (VMAT) plans by analyzing dose evaluating parameters and comparing with radiobiological parameters of dose - volume (DV) optimization based plans. In current study, the performance of DV - optimization based VMAT plans for 8 prostate cancer patients was done with standard dose - fractionation protocol in Eclipse 13.6 (VMS) treatment planning system where dose distribution were observed inherently non-uniform & then DV-gEUD plans were generated with same TPS version for comparison. All plans were created using the same 6MV Photon beam commissioned for Varian clinac DHX linear accelerator (VMS). The dose response evaluating parameters analyzed included conformity index (CI), homogeneity index (HI), TCP (Tumor Control Probability) and the different dose-volume indices of organs risk (OARs, including bladder, rectum &femoral heads), mean doses& the normal tissue complication probability (NTCP). As a result both plans have no significant changes for the coverage of target volume with conformity & homogeneity indices. However the DV- gEUD plan had the advantage of dose sparing for OARs. In the conclusion, the DV-gEUD plans gave superior dosimetric results for the treatment of prostate cancer in terms of PTV coverage & OAR sparing without compromising the homogeneity of dose distribution in the PVT.*

***Keywords: -** Dose planning, EUD, TPS, DV-optimization, dose evolution parameters.*

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I. Introduction

Prostate cancer is the second most common cancer & the sixth leading cause of cancer death among men worldwide. The cancer Projection data shows that the number of cases will become double by 2020[1]. In India, it is the second most common cancer in Indian males as per the Indian council of Medical Research (ICMR) &various state cancer registries. The incidence rate in India is 9-10/100000 population which is higher than other parts of Asia & Africa but lower than USA & Europe. It has been shown in randomized trails that many form of cancer have affective response to external beam radiation therapy with an escalated dose in the range of 75-81Gy, When compare to the conventional prescription of 70Gy [2, 3]. The difficulty in treatment planning for prostate cancer varies greatly case by case. Important issues have been raised concerning how to reduce the radiation dose to normal tissues, how to maintain a certain tumor control probability (TCP), and how to maintain the quality of life for prostate cancer patients. The proffered method for treating Prostate cancer patients with radiation is volumetric modulated arc therapy (VMAT), which rotates the gantry of the linear accelerator around the patient for a partial or full arc at a constant or variable rate. The MLC (Multi leaf collimator) are in constant motion with radiation beam on during the rotation, & the dose rate is continuously varied to weight the beam based on the gantry angle of linear accelerator. Most VMAT planning systems apply dose-volume (DV) based objective functions for dose optimization and an acceptable plan can be generated in most cases. For more complex plans, more iteration is required because many Parameters need to be finely tuned. A successful improvement tool-generalized equivalent uniform dose (gEUD) was developed with fewer parameters setting [4-8] to improve the quality of plans. However gEUD based optimization cannot demonstrate

such advantages on first run, more iteration are required to share the dose distribution [9]. To overcome the disadvantages mentioned above, here treatment planning started with DV-based optimization, and then improved it by adding gEUD-based improvement. Current study based on strategies and choice of volume effect parameters and weight age of cost function by standard recommendations. The goal was to reduce the number of iterations and to reprove the optimum dose distribution to target volumes and improving sparing of normal structure volumes surrounded by the target volumes. This method first determined the approximate solutions for most of the target volumes by DV based optimization then adjusted the DV histogram (DVH) by gEUD based optimization to obtain superior solution. This study also compared and evaluated the difference between two different methods for the treatment of Prostate cancer - DV plan and DV - gEUD plan - thus providing effective quantities indicator model for reference.

II. Method and Materials

Research Samples and Contouring:

All 8 patients were immobilized using thermoplastic cast in the supine position and patients were scanned using X-ray CT (Brilliance Big Bore 7483, Philips) with 5mm slice thickness containing 512 x 512 pixels per slice. Before CT Simulation bowel and bladder preparation was considered. With prostate radiation treatment, the planning target volume (PTV) was contoured by radiation oncologist using CT images by expanding each clinical target volume (CTV) as per standard recommendation [11]. To avoid inter observer variations in target volumes delineations; the same oncologist outlined all cases. The Characteristics of the patients were presented in Table-1.

Table - 1: Patient Characteristics (n=08). Data are reported for cohort of 08 patients.

CHARACTERISTIC	VALUES
AGE	45-65
PRESECRIBED DOSE	69.3(Gy)
NO OF FRACTIONS	33
PLANNING TARGET VOLUME(PTV)/VOLUME	
PTV (HIGH RISK)	55±15 cc
PTV (INTERMEDIATE RISK)	80±20 cc
PTV (LOW RISK)	1311±50 cc

Treatment planning (DV-Plans and DV-gaud Plans):

The VMAT based, DV Plans and DV-gEUD plans were generated with treatment planning system using Eclipse 13.6, Varian Medical systems (VMS) with photon optimization (PO) with maximum dose rate. All Plans were generated with 6MV Photon beam commissioned linear accelerator clinac DHX (Varian Medical System) equipped with a Millennium 120 leaf MLC(multileaf collimator) (Varian Medical Systems) with a leaf width of 5mm at the 150 centre for the Central 20 cm and 10 mm in the outer 20 cm with leaf speed 2.5 cms^{-1}. The dose prescription for the PTV was 69.3Gy per 33 fractions. The main object of treatment plans were to ensure that 95% of the prescribed dose covered 95% of the PVT, while restricting the dose for OAR as much as reasonably possible. The Overall work flow shown in Figure-1.The contouring of the Target volumes (PTV) and OARs (Organ at Risks) and evaluation of treatment plan were performed by same Radiation oncologist to avoid the inter observer variations while the treatment plans were carried out by the same medical physicist. The DV-based VMAT Plans were planned with coplanar arrangement and optimized with PO-module. The planning objective and constraints used for DV-plan work presented in Table-2.

Figure-1. Flow chart gEUD, generalized equivalent uniform dose, TPS treatment planning system.

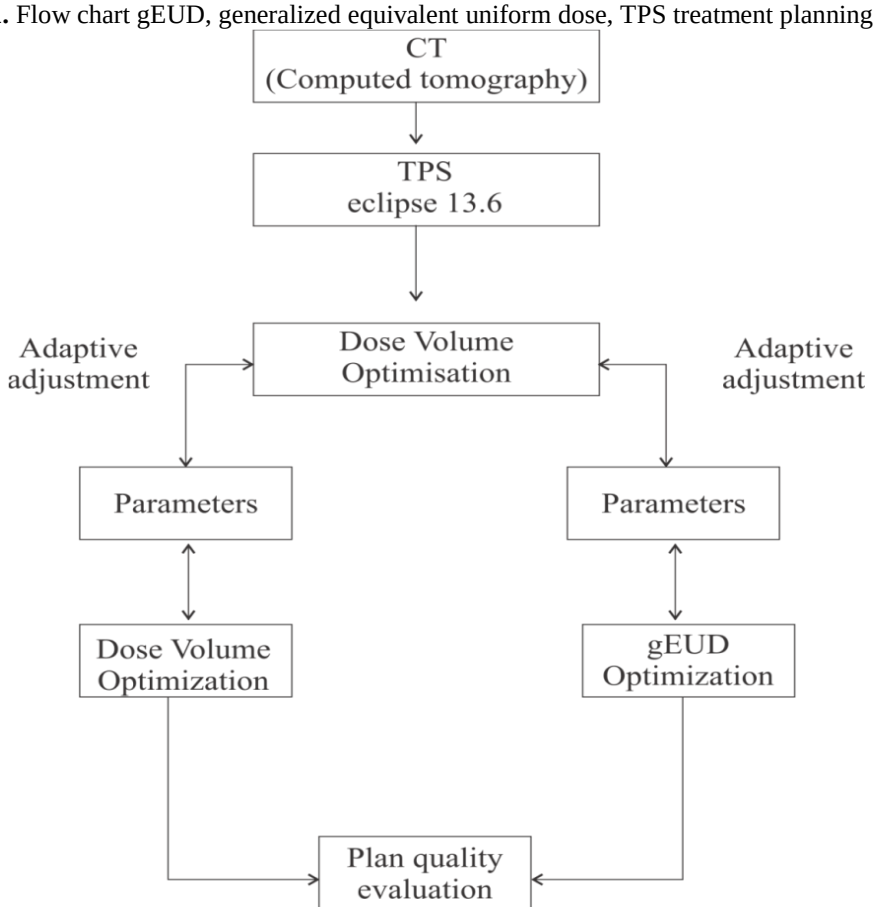

Table - 2 : Planning Objectives and Dose Constraints

Organ	DV-Plan	DV-gEUD Plan
PTV_{HR}	69.3Gy(Uniform dose) V95% >95%	69.3Gy(Uniform dose) V95% >95%, Target EUD=69.3Gy,a= -10
Bladder	V50Gy<65%,V65Gy<50%, V70Gy<35%	V50Gy<65%,V65Gy<50%, V70Gy<35%,EUDmax=58Gy,a=8
Rectum	V50Gy<60%,V65Gy<35%, V70Gy<25%	V50Gy<60%,V65Gy<35%, V70Gy<25%,EUDmax=59Gy,a=8
Femoral heads	D_{max}<50Gy,V50Gy<10%, V45Gy<20%,V40Gy<40%	D_{max}<50Gy,V50Gy<10%, V45Gy<20%,V40Gy<40% EUD max=45Gy,a=12

DV Plan, dose-volume based VMAT (Volumetric Modulated Arc Therapy) plan : DV-gEUD plan, dose - volume with generalized equivalent uniform dose based VMAT; PTV, planning target volume;' a' is volume effecting parameter; V_{xGy}, percent volume receiving $\geq x_{Gy}$ dose;$V_{z\%}$, volume receiving $\geq$ Z% of the prescribed dose.

In the DV-gEUD plan, the ordinary plan was added to a gEUD - objective to assess the optimization process [12], and objective setting parameters were same as those in DV-plans earlier. gEUD objective options can be generally selected in TPS (Varian Eclipse 13.6) as Target EUD selected for the PTV, while max. EUD selected for OARs. The resolution of the dose calculation grid bin size considered unbiased for subsequent computation of various indices.

Dose evaluation Parameters:

The DV Plan and DV-gEUD plans were compared as follows: for the PTV, the conformity index (CI), homogeneity index (HI) [13-15] and TCP were used; for the OAR, the Mean dose, DV-indicators, NTCP were used. The CI was used to evaluate the conformal coverage of the PTV by the isodose volume, prescribed in the treatment plan [13]. CI =$\frac{V_{PTV} \times V_{TV}}{TV_{PV}^2}$ (V_{TV}, volume of actual prescribed dose; V_{PTV}, volume of PTV; T_{VPV}, volume & V_{PTV} within V_{TV}); at CI=1, optimal treatment conformity is achieved. The HI was used to determine dose

homogeneity of the PTV. HI = $D_{5\%}$/ $D_{95\%}$ ($D_{5\%}$ and $D_{95\%}$ are the minimum doses delivered to 5% and 95% of the PTV, respectively).The larger the HI value, the lower the dose homogeneity.

Generalized Equivalent uniform dose (gEUD) :

The concept of equivalent uniform dose (EUD) proposed by Niemierko [4] in 1997, Li et al [16] and Deasy [17] provides a single metric for reporting non-uniform tumor dose distribution. It is defined as the uniform dose that, if delivered dose over the same number of fractions as the non-uniform dose distribution of interest, yields the same biological effect. To extend the Concept of EUD to normal tissues, Niemierko [5] in 1999, proposed a phenomenological formula referred to as the generalized EUD (DVH-based) or gEUD.

$$\text{gEUD} = (\sum V_i \, D_i^a)^{\frac{1}{a}}$$

Where V_i is the fractional organ volume receiving a dose D_i and "a" is a tissue - specific parameter that describes the volume effect. For a --> - ∞, gEUD approaches the minimum dose; thus negative values of "a" are used for tumour. For a --> + ∞, gEUD approached the maximum dose. For a=1, gEUD is equal to the arithmetic mean dose, fir a=0 gEUD is equal to the geometric mean dose. The gEUD is often used in plan evolution and optimization because the same functional form can be applied to both targets and OARs with a single parameter capturing the dosimetric essence of the biological response [18].

TCP/ NTCP:

The EUD-based TCP/NTCP formula [5, 19] derived by Niemierko was used [5, 20]

$\text{TCP} = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}}$ and $\text{NTCP} = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}}$

Where TCD_{50} is the absorbed dose producing a 50% control rate of the tumor exposed to uniform radiation, γ_{50} is the unit less model parameter for describing the slope of the tumor dos-response curve, and TD_{50} is the tolerance dose producing a 50% complication rate within a specific period of Home. In the current study, The TCP was calculated for target volume and NTCPs were calculated for OARs (Bladder, Rectum).

Dose - Volume indicators:

A. Observe the dose received by a specific volume of OAR as D_{xcc}, indicating Dose (Gy) in X CC Volume of organ. Different dose receiving volumes were observed separately for OARs.

B. Observe the volumes of OARs that receives a specific percentage of the dose as $V_{xx\%}$, denotes the volume percentage of the organ that received xx% of the prescribed dose. Here also different xx% dose receiving volumes are observed separately for OARs.
Generally, for the same volume or dose, The smaller the value of $V_{xx\%}$ or V_{xxGy}, the better the quality of the plan.

Statistical Analysis:

The difference between the DVH parameters of the DV-Plan and DV-gEUD plans were analyzed using a two-tailed exact paired t-test (each pair in the test consisted of patient - specific DVH values) Statistical Significance was set at $p \leq 0.05$. Statistical package for the social science (SPSS) Software was used for data processing.

III. Results

The planning Target volume (PVT) dose distribution(all axial dose distribution) of the DV-plan and Dv-gEUD plans for a typical case is shown is Figure- 2 ; The DVH is presented in Figure-3.The dosimetric results of PVT between DV and DV-gEUD plans were presented in Table-3. All plans were included in the present study were clinically acceptable. The CI, HI and TCP were observed similar in the two plans. Regarding total monitor units (MV) calculated. The DV-gEUD plan [650± 100 (550-750)] was significantly shorter than the DV-plan [750±100(650-850].

Table-3 : Dosimetric Results of PTV Between DV and DV-gEUD Plan

PARAMETER	DV PLAN	DV-gEUD PLAN	p-VALUE
V95%(%)	98.4±0.45 (98.85-97.95)	98.5±0.8(97.7-99.3)	NS
CI	0.86±0.15(0.71-1.01)	1.01±0.1 (0.91-1.11)	NS
HI	1.10±0.03 (1.07-1.15)	1.11±0.03(1.06-1.10)	NS
TCP(%)	89.80±2.5(92.3-87.3)	89.95±1.2 (88.45-91.45)	NS
MU	750±100(650-850)	650±100(550-750)	0.002

CI, Conformity index; HI, homogenate index; NS, not statically significant; PTV, planning target volume; TCP, Tumor control probability; MU, Monitor units; DV-plan, Dose-volume base VMAT plan DV-gEUD plan, dose-volume with generalized-Equivocator uniform dose based VMAT plan; $V_{x\%}$, volume receiving ≥ x% of the prescribed dose; stastical significant ($p<0.05$) is reported from a two-tailed exact paired t-test.

The DVHs for Bladder (Fig. 4a & 4b), Rectum (Fig. 5a & 5b), and Femoral heads (Fig. 6a & 6b) are presented respectively, while the results of dose - evolution are presented in Table-4, Table- 5 and Table-6 respectively.

Table-4: Dosimetric Results of Bladder (Volume = 220±100cc)

PARAMETER	DV PLAN	DV-gEUD PLAN	p-VALUE
MEANDOSE(Gy)	47.28±5.6	44.80±4.6	0.006
NTCP(%)	15±10.5	10.5±8.5	0.008
V30Gy(%)	92.4±3.5	84.6±5.0	0.0018
V50Gy(%)	46.19±2.5	40.6±2.5	0.0011
V65Gy(%)	2.85±0.5	3.05±0.6	NS
V5%(%)	100±0	100±0	NS
V10%(%)	100±0	100±0	NS
V50%(%)	85.0±6.0	72.1±4.0	0.003
V90%(%)	4.6±0.5	5.7±0.5	0.005
V100%(%)	0.1±0	0.1±0	NS
D1cc	71.5±0.5	70.5±0.6	NS
D5cc	66.95±0.4	68.6±0.5	NS
D10cc	64.5±0.3	63.5±0.3	NS
D50cc	56.3±1.0	54.2±1.5	NS
D100cc	51.5±2.5	49.5±3.6	0.002
D125cc	47.6±5.5	44.6±5.5	0.006
D150cc	43.6±9.6	39.09±8.0	0.006
D200cc	35.4±7.0	30.3±7.5	0.005
D220cc	32.5±4.0	26.8±2.0	0.001

CI, Conformity index; HJ, homogeneity index; NS, not statically significant; PTV, planning target volume; TCP, Tumor control probability; MU, Monitor units; DV-plan, Dose-volume base VMAT plan DV-gEUD plan, dose-volume with generalized-Equivocator uniform dose based VMAT plan; $V_{x\%}$, volume receiving ≥ x% of the prescribed dose; stastical significant ($p<0.05$) is reported from a two-tailed exact paired t-test. NTCP, normal tissue complication probability $V_{z\%}$, volume receiving ≥ Z% of prescribed dose. Dycc. dose of the Ycc volume.

In Table-4, the mean dose and NTCP of the bladder (volume=220±100 cc) were observed significant variation as higher than those in DV-gEUD plan indicating that DV-gEUD plan had better dose sparing for bladder. Also for the bladder, the doses for the different volume, as well as the volume receiving different. Percentage of the prescribed dose showed better performance in the DV-gEUD plan. In Table-5, The Dosimetric results of Rectum (Volume = 65±30cc) shows that mean dose and NTCP in DV-gEUD plan was better performance. Also in DV-indices, significant variation in ($P<0.05$) was seen in V_{30Gy}, V_{50Gy} and other intermediate volume (Table-5) showing that DV-gEUD plan has Superior dosimetric results. Similarly in Table-6, Statistical analysis of D-V-result of femur heads (Volume = 140±15cc) showing that significant variation in low-Dose receiving large volumes.

Table-5 Dosimetric Results of Rectum (Volume=65±30cc)

PARAMETER	DV PLAN	DV-gEUD PLAN	p-VALUE
MEANDOSE(Gy)	41.6±1.2	40.54±3.0	0.002
NTCP(%)	4.1±5.2	1.9±2.9	0.007
V30Gy(%)	73.5±2.4	70.5±2.0	0.0012
V50Gy(%)	51.5±5.5	44.2±4.5	0.0014
V65Gy(%)	5.5±0.5	6.0±1.0	NS
V5%(%)	100±0	100±0	NS
V10%(%)	88.5±1.0	88.2±1.5	NS
V50%(%)	70.50±9.5	67.1±8.0	0.009
V90%(%)	5.4±2.0	6.5±3.0	NS
V100%(%)	0.8±0.5	1.2±0.5	NS
D1cc	66.5±0.5	69.1±0.4	NS
D5cc	60.1±2.0	63.3±2.5	NS
D10cc	56±1.0	58.0±1.0	NS
D20cc	56.3±1.0	54.2±1.5	0.008
D30cc	52.5±6.0	48.3±5.5	0.003
D40cc	39.5±6.0	34.7±7.0	0.009
D50cc	10.±0.3	11.8±0.4	NS
D60cc	100±0	100±0	NS

Table-6 : Dosimetric Results of Femurheads (volume=140±15cc)

PARAMETER	DV PLAN	DV-gEUD PLAN	p-VALUE
MEANDOSE(Gy)	18.0±4.0	16.5±2.0	0.005
DOSE MAX	49.5±0.5	47.0±0.5	NS
V30Gy(%)	18.0±4.0	15.7±5.0	0.020
V40Gy(%)	3.4±0.5	3.7±0.5	NS
V45Gy(%)	0.5±0	0.5±0	NS
V50Gy(%)	0	0	NS
V5%(%)	100±0	100±0	NS
V10%(%)	81.9±2.0	76.5±2.5	0.003
V20%(%)	56.7±5.5	45.6±6.0	0.002
V30%(%)	35.5±4.0	31.9±4.0	0.005
V50%(%)	11.0±0.5	10.1±0.5	NS
D1cc	42.5±0.5	42.5±0.3	NS
D10cc	37.5±0.5	36.3±0.5	NS
D20cc	30.0±1.0	31.70±1.0	NS
D50cc	20.5±4.5	18.8±5.0	0.007
D70cc	16.5±4.0	12.1±3.0	0.002
D100cc	10.5±2.0	8.2±2.0	0.001
D120cc	56.3±1.0	54.2±1.5	0.0015
D140cc	2.0±1.0	2.0±1.0	NS

CI, Conformity index; HI, homogenate index; NS, not statically significant; PTV, planning target volume; TCP, Tumor control probability; MU, Monitor units; DV-plan, Dose-volume base VMAT plan DV-gEUD plan, dose-volume with generalized-Equivocator uniform dose based VMAT plan; $V_{x\%}$, volume receiving ≥ x% of the prescribed dose; stastical significant ($p<0.05$) is reported from a two-tailed exact paired t-test.

IV. Discussion

In the treatment planning process, it is necessary to reduce the dose to normal tissues while maintaining tumor control. This must be achieved within a reasonable planning time currently most inverse planning (VMAT) is performed using DV-based constraints. Multiple or Single DV constraints used for inverse treatment planning are based on clinical studies that demonstrate correlation between tumor control/Complication incidence and particular DV metrics. The main limitation associated with this approach is Specifying multiple DV-Constraints increase computational complicity of planning problem. Moreover, cost functions based on DV-constraints can lead to multiple local minima. This implies that a search algorithm designed for global minimum problems is likely to get trapped in a local minimum, potentially leading to less favorable dose distributions. It can be beneficial to treat EUD-based cost functions as hard constraints because they are directly associated with control/complication risks On the other hand, the definition of EUD allows for a certain freedom in shaping the dose distribution. Therefore, EUD constraints are less restrictive than multiple DV-constraints and offer in here best trade off between different dose levels, allowing controlled violations for some DV-constraints, while [11] over fulfilling other constraints to generate overall better dose distribution. Currently most of the inverse treatment planning systems (TPS) is using DV-based constraints. The gEUD objections function is optimal. Wu et al [9] proposed combining gEUD - based and DV - based optimization approbation to overcome Dose-Volume optimization (DVO) imitations. In our study, we started with a DV-generated plan then improved it by adding gEUD based improvements to overcome the disadvantages of DVO. The goal was to reduce the number of iterations and to improve the optimum dose distribution by utilizing the DV optimization module with gEUD. The DV-gEUD plans gave superior dosimetric results regarding OAR sparing and total number of monitor units than the DV-plans, without sacrificing the homogeneity of dose distribution in the PTV. In terms of quality assurance verification, the results of the DV-plan and the DV-gEUD plan had similar pass rates, indicating that the DV-gEUD plan is an acceptable option.

It is noteworthy that the DV-based plan used in the present study in clinically acceptable. In a non-typical planning process, with reasonable objectives and acceptable criteria, once the objective and criteria are met, VMAT plan optimization in the next level of dose calculation with enough patience and effort, a better plan might be obtained through repeated DV-based optimization, similar to that achieved with the DV-gEUD plan. The ultimate goal of the present study was to obtain a better treatment plan in a more efficient way. Additionally particular attention was taken to reducing bias during the planning (TPS). The dose plans were approved by the same oncologist, who reviewed all of the plans.

V. Conclusion

A better result, obtained by starting with DV-generated plan and then improving it by adding gEUD-based improvement can reduce the number of trails and errors and also improve the optimum dose distribution. The

DV-gEUD plans gave Superior dosimetric results for treating prostate cancer in terms of PTV Coverage and OAR sparing than DV-plans, without sacrificing the homogeneity of PTV-dose distribution.

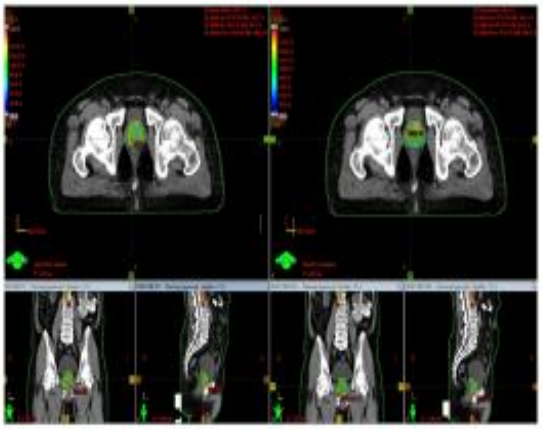

Figure- 2 The planning Target volume (PVT) dose distribution(all axial dose distribution) of the DV-plan and Dv-gEUD plans for a typical case is shown.

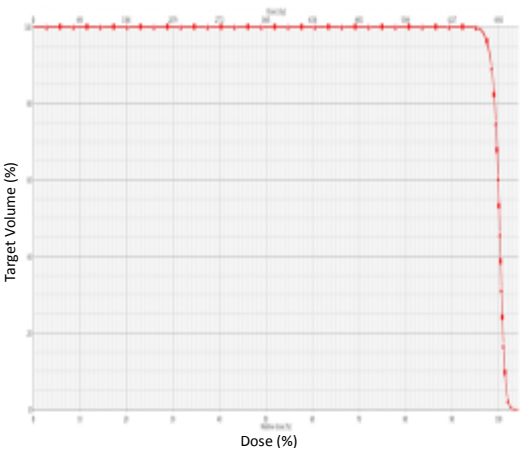

Figure-3. The DVH presentation of PTV

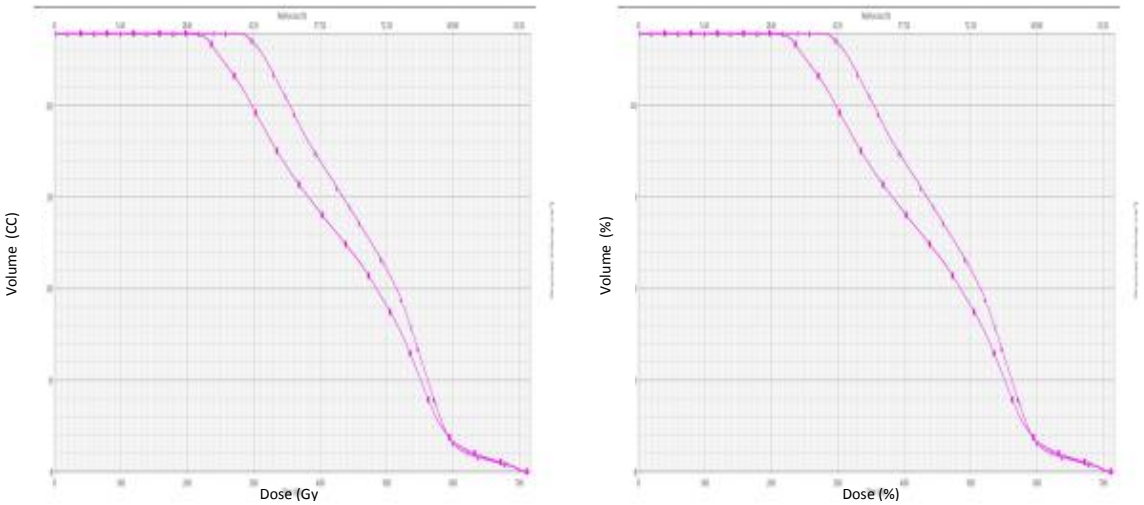

Figure. 4a & 4b.The absolute and relative dose-volume indicators for Bladder

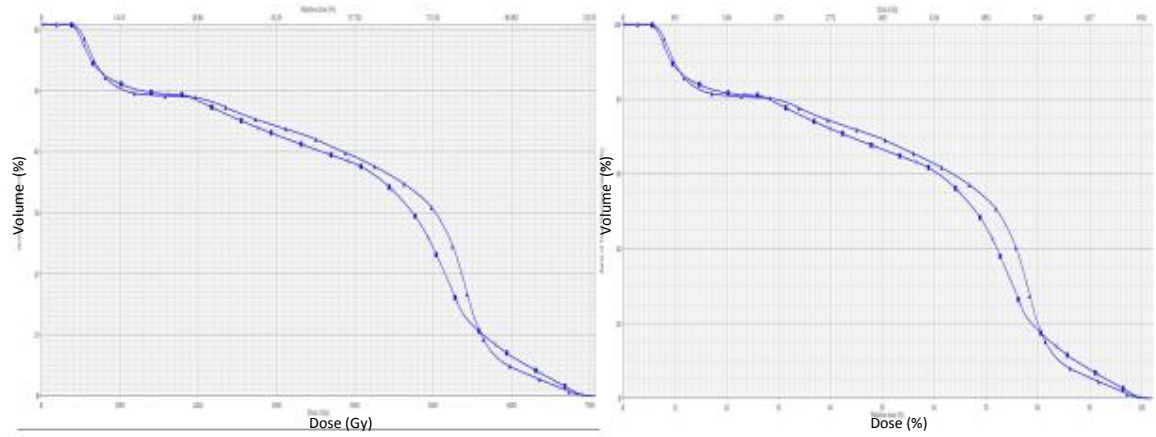

Figure. 4a & 4b.The absolute and relative dose-volume indicators for Rectum

DV-Plan DVH, g EUD -DV-Plan DVH)

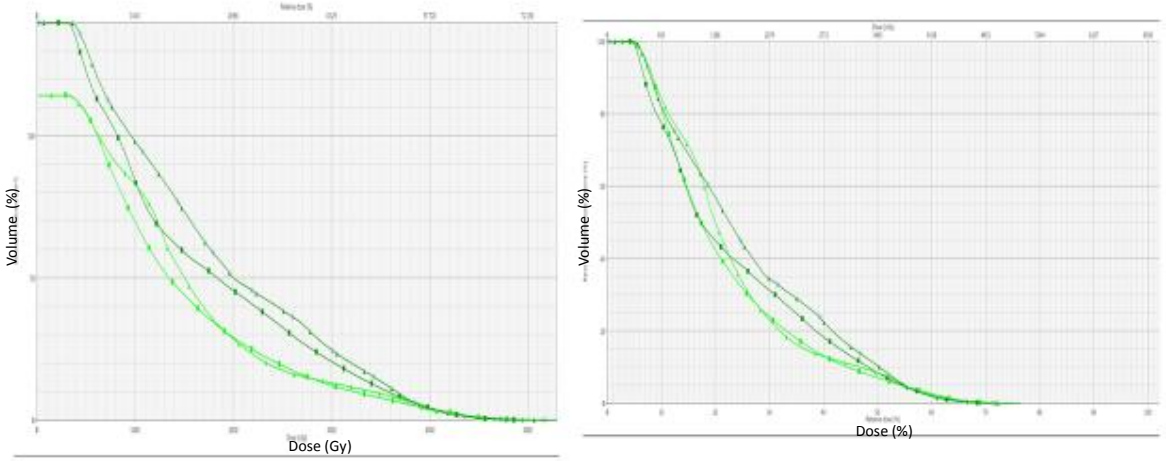

Figure. 4a & 4b.The absolute and relative dose-volume indicators for Femuralheads

DV-Plan DVH, g EUD- DV-Plan DVH)

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