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The Dosimetric Comparison of Different SBRT Techniques for Treatment of Liver Cancer Using Flattened and Flattening Filter Free Beam

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ABSTRACT

Introduction:To compare the three-dimensional conformal radiotherapy (3DCRT), dynamic conformal arc therapy (DCA), and volumetric modulated arc therapy (VMAT) in stereotactic body radiation therapy (SBRT) of liver cases using 6MV and 10 MV flattened beam (FB) and flattening filter-free beam (FFFB).

Material and Methods:Twenty liver SBRT patients were selected. The dose prescription was 40 Gy delivered in 5 fractions. 3DCRT, DCA and VMAT planning was performed using 6 MV FB, 6 MV FFFB, 10 MV FB and 10 MV FFFB. Planning target volume (PTV) coverage, organs at risk (OARs) doses, monitor units (MU), and beam on time (BOT) were noted.

Results:VMAT plan produces better PTV coverage in the $D_{98\%}$ and $D_{95\%}$ region. 6 MV and 10 MV VMAT FB and FFFB reduced the D_{700cc}, V_{10Gy}, and D_{mean} of the liver minus gross tumor volume region compared to 3DCRT and DCA plans. FFFB in combination with VMAT producing highly conformal plan (Conformit index=1.19), better conformity number (CN=0.85), and lowering Paddick gradient index (GIpad=3.29) in comparison to 3DCRT and DCA. The FFFB needs higher monitor units to achieve the plan in all the techniques. FFFB reduces the BOT, body-PTV mean dose in the non-tumour volume.

Conclusion: VMAT combined with FFFB will produce a highly conformal plan, spare the OAR's, deliver fast and dose fall off in the body-PTV region is more as compared to 3DCRT and DCA. The VMAT will more advantage to treat the multiple lesions simultaneously and reducing the intra-fraction motion error in liver SBRT.

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Introduction

Stereotactic body radiation therapy (SBRT) plays an essential role in treating primary and metastatic liver tumours. SBRT improves local control rates, reduced toxicity, better survival, and enhances the quality of life. SBRT technique utilizes high doses of radiation delivered precisely in one to six fractions, giving the high biologically effective dose [1]. Recent technical improvements in imaging, treatment planning system, treatment techniques, treatment equipment [2,3], and motion management system will increase the use of clinical use of SBRT. However, the irradiation of normal liver will increase the risk of radiation-induced liver diseases (RILD). Radio-biologically, the liver is a parallel organ, and the RILD is directly proportional to the liver mean dose [4].

Historically, the flattened beam (FB) is used in two-dimensional and three-dimensional conformal radiotherapy. Recently, the advances in treatment techniques like intensity-modulated radiotherapy (IMRT) and Volumetric modulated arc therapy (VMAT) will capable of producing the conformal plans and do not need of FB directly due to the availability of optimization concept in the treatment planning system will generate the desired fluence by modifying the multi leaf collimator (MLC) speed, dose rate, and gantry speed to achieve the plan goal [5].

Recently, modern linear accelerators have 6 MV, and 10 MV FB and FFFB. The flattening filter free beam (FFFB) has unique features [6] like less head scatter, reduction in out of field dose, sharper penumbra, [7,8] energy spectrum variation in the off-axis position is minimum, increased dose rate, reduced beam on time (BOT), less multileaf collimator (MLC) leakage, less electron contamination, improving the dose calculation accuracy[9], reduced the structure shielding requirements[10] and lower neutron level contamination in higher energies (>10 MV) compared to FB.Kry SF et al. [11,12], reported that the second cancer malignancy risk is depends upon the treatment energies, using 6 MV for IMRT planning, the risk rate is 2.9% and 5.1% for 18 MV IMRT plan.Further using FB for planning, the risk rate

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is 2.9% and in the case of FFF beam, the risk is reduced to 0.9%.

Worms ES et al. [13] reported that the intra-fraction motion in liver cases is due to diaphragmatic movement. The motion is predominantly in a cranio-caudal direction. The mean 3D intra-fraction and intra-field motions were 17.6 mm (range, 5.6 - 39.5 mm) and 11.3 mm (2.1 - 35.5 mm), respectively.

Munirathinam N et al.[14] studied the deep inspiration breath hold technique in liver SBRT cases and the observed the average breath hold time is 25-30 seconds. The mean number of breath holds is reduced in FFFB (3.3 ± 1.9) as compared to FB (9.7 ± 3.2) and to deliver the prescribed dose faster in moving target, the FFFB is recommended. FFFB will help to reduce the patient discomfort and the chance of inter fraction motion error.

High conformity and sharp dose falloff outside the PTV is essential in SBRT planning. Recently the use of FFFB and dynamic conformal arc (DCA) technique use is increased. Reggiori et al. [15] compared the 10 MV FB and FFFB in SBRT liver cases, using VMAT, the study result showed that the 10 MV FFFB VMAT reduces the healthy tissue mean dose is about 1.3% and healthy liver mean dose is about 1.1% as compared to 10 MV FB VMAT. Further the FFFB reduces the BOT of 73% as compared to FB (2.2 vs.8.2 min).

Young Min Moon et al. [16] compared the DCA and VMAT in liver SBRT cases using Eleka Infinity linear accelerator (Elekta AB, Stockholm, Sweden) and the beam energy chosen is 6 MV FB.The planning is performed in MONACO treatment planning system (TPS) (Version 5.1) and Monte carlo algorithm is used for calculation. The study concluded that the DCA is alternative to VMAT. DCA plan needs shorter calculation time (14.4 vs. 29 min),lesser monitor unit (MU) (2444 vs.2741 MU) and reduced the delivery time (3.6 vs. 4.5 min) as compared to VMAT.

The scientific community already studied the above physical advantage of FFF beam and the planning outcome of FFFB vs. FB to be analyzed. The present study will compare the three dimentional conformal radiation therapy (3DCRT), DCA, VMAT in terms of PTV coverage, organ at risk sparing (OAR's), MU, BOT and different dosimetric indexes. Further this study will investigate which treatment technique is suitable for liver SBRT cases using FB and FFFB.

Materials and Methods

Twenty liver SBRT patients were selected randomly. Patients were supine with their arms kept above the head and immobilized using a vacuum cushion (Orfit Industries, Belgium). The Siemens Somatom Sensation (Siemens Medical Solutions, Malvern, PA) CT scanner was used to acquire contrast-enhanced four dimensional computed tomography images [17] (4D-CECT) at 2mm slice thickness. For contouring and planning, the 4D-CECT images were transferred to the Varian Eclipse treatment planning system, Version 11.0 (Siemens Healthineers, Erlangen, Germany). The planning was performed on average 4D-CECT. The gross tumor volume (GTV) includes macroscopic disease, and the clinical target volume is the same as GTV. The planning target volume (PTV) is generated from clinal target volume (CTV), which contains the internal margin and setup margin. The CTV to PTV margin is in the range of 5-8mm. like normal liver and spinal cord, the GTV, PTV, and OAR's were contoured by a Radiation oncologist.

According to The Radiation Therapy Oncology Group (RTOG), protocol 1112 [18] and The American Association of Physicists in Medicine (AAPM) report 101 [19], the below-mentioned dose constraints were followed for PTV and OAR's. The planning goal was for the prescription dose to cover 95% volume of PTV. The maximum dose within the PTV is limited to 150%. The dose constraint to liver-GTV was D_{mean} is 15Gy, V_{10Gy} = 70%, and D_{700cc} = 15Gy [20]. The maximum dose (D_{max}) to the spinal cord is <18 Gy. The spinal cord $V_{0.35cc}$ and $V_{1.2\ cc}$ dose is 23 Gy and 14.5Gy. The dose to skin $V_{0.5cc}$ and V_{10cc} is 32Gy and 36.5Gy, respectively.

3DCRT, DCA, and VMAT plans were generated on the Varian Eclipse treatment planning system (Version 11.0) using a Varian True beam linear accelerator (Siemens Healthineers, Erlangen, Germany)inbuilt with a high definition Millennium multi-leaf collimator. The system can deliver 6 MV, 10 MV FB, and FFFB. The dose rate for 6 MV, 10 MV FB is 600MU/min, 1400MU/min for 6 MV FFFB and 2400MU/min for 10 MV FFFB. The final dose calculation is performed in Analytical Anisotropic Algorithm, and the dose calculation grid size is set to 2mm. 3DCRT plan consists of nine beams, and the beam angles were 10°, 50°, 80°, 180°, 210°, 240°, 280°, 310°, and 340°. The dynamic conformal arc and VMAT plan consist of two partial arcs placed in clockwise (181° - 80°) and counterclockwise direction (80° - 181°). The MLC is fitted dynamically to the PTV outline in all gantry rotations in dynamic conformal arc plans. The beam placement arrangement is shown in Figure1.

The treatment delivery parameters like MU, BOT were noted. Dose to PTV and OAR's (liver-GTV, spinal cord, skin, and body-PTV) were noted from the cumulative dose volume histogram (cDVH). The conformity index (CI), homogeneity index (HI), conformation number(CN), gradient index (GI), gradient score index (CGIg) high and low gradient index (HGI & LGI) were calculated. The formulas are mentioned in Table 1. The statistical analysis was performed using SPSS software (V20.0). The statistical significance between the two groups was found out using paired sample t-test method. $P \leq 0.05$ is considered statically significant.

Figure 1. Beam placement of 3DCRT (left) and DCA/VMAT planning (right).

Table 1.Various definitions of conformity index (CI), homogeneity index (HI) and gradient indexes.

S.No.	Formula	Ideal Value	Reference	Description
1	RTOG Conformity index (CI_{RTOG}) $=\frac{VRI}{TV}$	1.0	Shaw E et al. [21]	TV_{RI}=Target volume covered by the reference isodose
2	Healthy tissue conformity index$=\frac{TVRI}{VRI}$	0-1	Lomax &Scheib et. al. [22]	V_{RI}=Volume of the reference isodose
3	$CI_{SALT}=\frac{TVRI}{TV}$	1.0	SALT Group [23]	CN= Conformation number
4	$CN=\frac{TVRI}{TV}X\frac{TVRI}{VRI}$	0.6-1.0	Van'tRiet et al [24]	TV: Target volume.
5	$HI_{ICRU}=\frac{D2\%-D98\%}{D50\%}$	0.0	ICRU 62 [25]	$D_{98\%}$, $D_{95\%}$, $D_{50\%}$, $D_{5\%}$ & $D_{2\%}$ are the doses to 98%, 95%, 50%, 5% & 2% volume of planning target volume.
6	$HI=\frac{D5\%}{D95\%}$	1.0	Kataria T et al. [26]	D_{max} is the maximum dose in PTV
7	$HI_{RTOG}=\frac{Dmax}{Dmin}$	1.0	Shaw E et al.	D_{min} is the minimum dose in PTV
8	$HI_{RTOG}=\frac{Imax}{RI}$	≤ 2.0	Shaw E et al.	GI is Gradient index HGI is High Gradient index
9	$GI=\frac{\text{half the prescription isidose volume (PIV0.5)}}{\text{Prescription isodose volume (PIV)}}$	≥ 3.0	Paddick et al. [27]	LGI is Low Gradient index I_{max} is the maximum dose in the planning target volume
10	$HGI=\frac{V50\%\ \text{Prescrtion Dose}}{V90\%\ \text{Prescrtion Dose}}$	≥ 3.0	Paddick et al.	RI is the reference isodose
11	$LGI=\frac{V25\%\text{Prescrtion Dose}}{V50\%\text{Prescrtion Dose}}$	≥ 3.0	Paddick et al.	$V_{90\%}$, $V_{50\%}$, &$V_{25\%}$ were volume receiving 90%, 50%, and 25% of the prescription dose
12	CGIg = 100- {100.[($R_{Eff,50\%Rx}$- $R_{Eff,Rx}$) - 0.3 cm]}	50-100	Wagner TH et al. [28]	CGIg is gradient score index
13	$R_{50\%}=\frac{V50\%\ \text{Prescrtion Dose}}{\text{Volume of PTV}}$	RTOG 0813	Bwzjak A et al. [29]	$R_{Eff,\ Rx}$ and $R_{Eff,50\%Rx}$ are the effective radius of the prescription isodose volume and one-half of the prescription isodose volume.
14	NTID = (non-tumor tissue volume) x (mean dose)		D'Souza WD et al. [30]	CGIg value 50 and 100 corresponds to minimum and maximum conformity. NTID is non-tumor integral dose

Results

The PTV size ranged from 15.1 to 324.7cc (average: 93 cc), and cDVHwere used to evaluate the treatment plans. The dose to PTV, OAR's doses (Liver-GTV, skin, spinal cord, and body-PTV), NTID, MU, BOT, CI, HI, CN, GI, $R_{50\%}$, D_{2cm}, HGI, and LGI were summarized in Table 2-3. The isodose distribution of one patient in the transverse slice for 6 MV FB, 6 MV FFFB, 10 MV FB, and 10 MV FFFB for 3DCRT, DCA, and VMAT plans were shown in Figure 2-3. Similarly, the cDVH for one patient is shown in Figure 4 for the 3DCRT, DCA, and VMAT techniques.

The PTV coverage in $D_{98\%}$, $D_{95\%}$region, and OAR's dose is better in VMAT as compared to 3DCRT and DCA plans. The $D_{95\%}$ value for 6 MV is 38.79 vs. 38.84 Gy (p=0.647), 39.04 vs. 38.95 Gy (p =0.342) and 40.04 vs. 40.06 Gy (p= 0.678) for 3DCRT, DCA and VMAT plans as compared to 6 MV FB vs. FFFB. The 10MV, $D_{95\%}$ is 38.54 vs. 38.43 Gy, (p = 0.250) for 3DCRT, DCA is 38.72 vs. 38.62 Gy, (p =0.364)and 39.83 vs. 40.01 Gy, (p= 0.376) for VMAT plan as compared to 10 MVFB vs. FFFB. The global maximum is higher in FFFB calculated DCA plans. The D_{max} for 6 MV DCA is 116.2 vs. 117.7 %, p=0.00, and in the case of 10 MV DCA, FFFB is 112.34 vs. 115.71 %, (p=0.00).

The values ofD_{700cc} ,$V_{30\%}$,$V_{50\%}$, V_{10Gy},and D_{mean} of Liver-GTV region is lower in VMAT than 3DCRT and DCA plans. The liver-GTV, D_{mean} value were 10.4 vs. 10.55 Gy (p = 0.014), 10.61 vs. 10.65 Gy (p =0.651) and 8.86 vs. 8.9 Gy (p= 0.043) for 3DCRT, DCA and VMAT plan as compared to 6 MV FB vs. FFFB. Similarly the D_{mean} value for 10 MV is 10.08 vs. 10.53Gy (p=0.752), 10.38 vs. 10.61 Gy (p= 0.00) and 7.50 vs. 7.55Gy (p=0.00) for 3DCRT, DCA and VMAT plan as compared to 10 MV FB vs. FFFB.

Table 2.PTV ,OAR's dose and various indexes comparison between 6MV FB / FFFB for 3DCRT, DCA, and VMAT plans. Dmax: maximum dose, Dmean: mean dose, FB: flattened beam, and FFFB: flattening filter-free beam.

Target and OAR's	Parameters	Mean ± SD						p- value (6MV FB vs FFFB)		
		6MV_3D_FB	6MV_3D_FFFB	6MV_DCA_FB	6MV_DCA_FFFB	6MV_VMAT_FB	6MV_VMAT_FFFB	3DCRT	DCA	VMAT
PTV	D98% (Gy)	38.11 ± 0.40	38.12 ± 0.66	38.28 ± 0.79	38.16 ± 0.76	39.66 ± 0.83	39.69 ± 0.82	0.959	0.282	0.616
	D95% (Gy)	38.79 ± 0.45	38.84 ± 0.66	39.04 ± 0.70	38.95 ± 0.65	40.04 ± 0.65	40.06 ± 0.62	0.647	0.342	0.678
	Dmax (%)	109.8 ± 1.13	111.81 ± 1.49	116.2 ± 2.46	117.7 ± 2.58	114.96 ± 1.35	115.74 ± 1.38	0.000	0.000	0.623
CONFORMITY INDEX	CI_{RTOG}	1.43 ± 0.11	1.28 ± 0.09	1.39 ± 0.17	1.39 ± 0.16	1.19 ± 0.15	1.19 ± 0.14	0.000	0.900	0.724
	Lomax and Scheib	0.67 ± 0.06	0.74 ± 0.04	0.7 ± 0.07	0.7 ± 0.07	0.82 ± 0.10	0.83 ± 0.08	0.000	0.839	0.041
	CI_{SALT}	0.96 ± 0.03	0.96 ± 0.03	0.96 ± 0.03	0.96 ± 0.03	0.96 ± 0.03	0.98 ± 0.02	0.399	0.267	0.007
CONFORMATION NUMBER	CN	0.65 ± 0.06	0.71 ± 0.05	0.68 ± 0.06	0.67 ± 0.07	0.79 ± 0.11	0.82 ± 0.07	0.000	0.880	0.015
HOMOGENEITY INDEX	HI_{ICRU}	0.13 ± 0.02	0.14 ± 0.03	0.17 ± 0.04	0.18 ± 0.05	0.09 ± 0.03	0.09 ± 0.03	0.016	0.034	0.330
	HI_{RTOG} =DMAX/RI	1.09 ± 0.03	1.11 ± 0.04	1.16 ± 0.06	1.17 ± 0.06	1.14 ± 0.03	1.14 ± 0.03	0.000	0.000	0.605
	HI_{RTOG} = Dmax/Dmin	1.24 ± 0.04	1.26 ± 0.06	1.31 ± 0.11	1.34 ± 0.12	1.31 ± 0.12	1.31 ± 0.12	0.003	0.000	0.683
	HI =D5/D95	1.11 ± 0.02	1.13 ± 0.03	1.16 ± 0.04	1.17 ± 0.05	1.07 ± 0.02	1.07 ± 0.03	0.007	0.073	0.016
HIGH & LOW GRADIENT INDEX	HGI	2.77 ± 0.17	2.87 ± 0.27	2.68 ± 0.20	2.72 ± 0.25	2.59 ± 0.17	2.61 ± 0.18	0.006	0.135	0.010
	LGI	4.45 ± 1.05	4.48 ± 1.08	3.31 ± 0.61	3.44 ± 0.81	3.45 ± 0.63	3.5 ± 0.69	0.041	0.266	0.037
GI PADDICK INDEX	GIpad	4.36 ± 0.79	4.37 ± 0.86	3.88 ± 0.67	3.95 ± 0.88	3.29 ± 0.31	3.28 ± 0.31	0.824	0.449	0.627
$R_{50\%}$	$R_{50\%}$	4.03 ± 0.38	4.25 ± 0.57	4.23 ± 0.65	4.32 ± 0.70	3.38 ± 0.46	3.41 ± 0.45	0.006	0.286	0.046
GRADIENT SCORE INDEX (CGIg)	CGIg	78.3 ± 11.16	76.15 ± 13.43	84.77 ± 11.57	82.28 ± 12.45	86.19 ± 11.31	84.77 ± 12.10	0.132	0.115	0.000
D_{2CM}	Dmax (%)	70.05 ± 4.47	70.43 ± 4.33	72.53 ± 5.76	73.04 ± 5.87	59.68 ± 2.47	60.36 ± 2.44	0.607	0.504	0.007
LIVER-GTV	D_{700cc} (Gy)	8.46 ± 5.74	8.7 ± 5.92	8.29 ± 5.89	8.35 ± 6.04	6.33 ± 4.59	6.4 ± 4.68	0.000	0.486	0.126
	V50% (Gy)	7.13 ± 5.74	7.26 ± 5.88	7.17 ± 5.98	7.18 ± 6.09	5.13 ± 4.09	5.17 ± 4.20	0.040	0.948	0.290
	V30% (Gy)	13.27 ± 5.85	13.5 ± 6.02	12.98 ± 6.61	13.09 ± 6.64	10.65 ± 4.95	10.69 ± 5.06	0.048	0.455	0.450
	V10Gy (%)	43.86 ± 18.97	44.29 ± 0.18	41.14 ± 21.17	41.4 ± 20.93	33.74 ± 14.60	33.93 ± 14.75	0.027	0.646	0.093
	Dmean (Gy)	10.4 ± 4.56	10.55 ± 4.63	10.61 ± 5.02	10.65 ± 5.04	8.86 ± 3.45	8.9 ± 3.48	0.014	0.651	0.043
SPINAL CORD	Dmax (%)	8.35 ± 4.61	8.14 ± 4.78	7.58 ± 2.66	7.3± 2.67	7.14 ± 3.60	6.84 ± 3.60	0.144	0.355	0.689
	V0.35cc (Gy)	7.38 ± 4.24	7.23 ± 4.40	6.59 ± 3.23	6.41 ± 3.20	6.4 ± 2.30	6.31 ± 2.41	0.144	0.406	0.454
	V1.2cc (Gy)	6.55 ± 3.98	6.45 ± 4.11	6.1 ± 2.99	5.85 ± 2.90	5.80 ± 2.09	5.78 ± 2.24	0.254	0.637	0.469
SKIN	V0.5cc (Gy)	22.59 ± 12.29	22.14 ± 12.04	21.51 ± 14.23	21.3 ± 14.25	19.78 ± 12.79	19.46 ± 12.35	0.000	0.000	0.000
	V10cc (Gy)	17.41 ± 12.83	17.13 ± 12.78	17.30 ± 14.20	17.12 ± 14.13	15.72 ± 13.03	15.2 ± 12.76	0.000	0.000	0.000
BODY-PTV	Dmean (Gy)	2.05 ± 0.77	2.03 ± 0.77	2.03 ± 0.65	2.01 ± 0.82	1.76 ± 0.65	1.74 ± 0.68	0.028	0.133	0.002
	1Gy (%)	24.8 ± 8.16	24.5 ± 8.25	25.95 ± 8.83	25.93 ± 8.99	23.9 ± 7.77	23.7 ± 7.86	0.001	0.473	0.980
	2Gy (%)	17.92 ± 6.35	17.74 ± 6.25	18.6 ± 6.54	18.3 ± 6.51	17.36 ± 6.02	17.1 ± 5.96	0.001	0.001	0.000
	3Gy (%)	14.17 ± 5.21	14.07 ± 5.14	15.24 ± 5.42	14.99 ± 5.40	14.22 ± 5.16	13.99 ± 5.01	0.095	0.008	0.000
	4Gy (%)	12.3 ± 4.57	12.26 ± 4.49	13.15 ± 4.77	13 ± 4.76	12.07 ± 4.53	11.93 ± 4.38	0.174	0.033	0.010
	5Gy (%)	11.3 ± 4.15	11.28 ± 4.07	11.60 ± 4.39	11.57 ± 4.34	10.4 ± 4.05	10.36 ± 3.94	0.648	0.993	0.377
Monitor Unit	MU	1286 ± 123	1405 ± 159	1369 ± 5.8	1576 ± 684	3231 ± 426	3368 ± 476	0.000	0.068	0.003
Beam on Time	BOT	2.14 ± 0.21	1.00 ± 0.11	2.74 ± 1.08	1.22 ± 0.43	6.46 ± 0.85	2.81 ± 0.40	0.00	0.00	0.00
Normal tissue integral dose	$x10^3$Gycc	37.68 ± 15.52	37.31 ± 17.72	37.35 ± 13.65	36.94± 15.96	32.34± 17.82	31.98 ± 13.90	0.028	0.133	0.002

Table 3. PTV, OAR's dose and various indexes comparison between 10MV FB / FFFB for 3DCRT, DCA, and VMAT plans. Where Dmax: maximum dose, Dmean: mean dose, FB: flattened beam, and FFFB: flattening filter free beam

Target and OAR's	Parameters	Mean ± SD						p- value (10MV FB vs FFFB)		
		10MV_3D_FB	10MV_3D_FFFB	10MV_DCA_FB	10MV_DCA_FFFB	10MV_VMAT_FB	10MV_VMAT_FFFB	3DCRT	DCA	VMAT
PTV	D98% (Gy)	37.69 ± 0.46	37.44 ± 0.55	37.86 ± 0.84	37.7 ± 0.55	39.39 ± 1.17	39.64 ± 0.81	0.018	0.194	0.313
	D95% (Gy)	38.54 ± 0.49	38.43 ± 0.60	38.72 ± 0.66	38.62 ± 0.60	39.83 ± 0.97	40.01 ± 0.63	0.250	0.364	0.376
	Dmax (%)	108.92 ± 0.97	113.15 ± 1.48	112.34 ± 1.44	115.71 ± 1.48	113.9 ± 1.72	114.65 ± 1.10	0.000	0.000	0.753
CONFORMITY INDEX	CI_{RTOG}	1.21 ± 0.07	1.29 ± 0.10	1.3 ± 0.14	1.35 ± 0.10	1.17 ± 0.12	1.19 ± 0.15	0.000	0.667	0.791
	Lomax and Scheib	0.8 ± 0.10	0.73 ± 0.05	0.73 ± 0.06	0.7 ± 0.05	0.83 ± 0.08	0.83 ± 0.08	0.000	0.017	0.500
	CI_{SALT}	0.97 ± 0.13	0.98 ± 0.04	0.95 ± 0.04	0.96 ± 0.04	0.98 ± 0.04	0.98 ± 0.03	0.004	0.585	0.708
CONFORMATION NUMBER	CN	0.79 ± 0.24	0.69 ± 0.04	0.7 ± 0.06	0.74 ± 0.04	0.82 ± 0.08	0.85 ± 0.07	0.834	0.903	0.369
HOMOGENEITY INDEX	HI_{ICRU}	0.13 ± 0.02	0.18 ± 0.03	0.16 ± 0.04	0.18 ± 0.03	0.10 ± 0.04	0.08 ± 0.03	0.072	0.719	0.776
	HI_{RTOG} =DMAX/RI	1.08 ± 0.02	1.13 ± 0.04	1.12 ± 0.04	1.15 ± 0.04	1.14 ± 0.04	1.13 ± 0.03	0.000	0.000	0.065
	HI_{RTOG} = Dmax/Dmin	1.25 ± 0.03	1.32 ± 0.06	1.3 ± 0.09	1.35 ± 0.06	1.31 ± 0.12	1.29 ± 0.11	0.000	0.000	0.654
	HI =D5/D95	1.11 ± 0.02	1.16 ± 0.03	1.14 ± 0.03	1.18 ± 0.03	1.08 ± 0.03	1.07 ± 0.02	0.000	0.000	0.127
HIGH & LOW GRADIENT INDEX	HGI	2.72 ± 0.14	2.74 ± 0.14	2.68 ± 0.19	2.7 ± 0.14	2.54 ± 0.19	2.56 ± 0.17	0.000	0.000	0.076
	LGI	4.17 ± 0.82	4.24 ± 0.88	3.19 ± 0.46	3.20 ± 0.88	3.27 ± 0.47	3.29 ± 0.53	0.267	0.144	0.177
GI PADDICK INDEX	GIpad	4.79 ± 0.76	4.22 ± 0.82	4.76 ± 0.86	4.09 ± 0.82	3.46 ± 0.85	3.29 ± 0.35	0.042	0.345	0.277
$R_{50\%}$	$R_{50\%}$	3.85 ± 0.36	4.15 ± 0.43	4.06 ± 0.60	4.29 ± 0.43	3.37 ± 0.46	3.39 ± 0.51	0.000	0.000	0.270
GRADIENT SCORE INDEX (CGIg)	CGIg	86.51 ± 8.87	84.05 ± 9.04	87.87 ± 9.81	86.9 ± 9.04	89.61 ± 9.37	89.44 ± 9.58	0.001	0.001	0.464
D2CM	Dmax (%)	68.78 ± 4.39	71.12 ± 3.85	70.46 ± 5.29	72.92 ± 3.85	58.73 ± 2.85	59.76 ± 2.64	0.002	0.000	0.503
LIVER-GTV	D_{700cc} (Gy)	8.09 ± 5.52	8.44 ± 5.77	8.02 ± 5.60	8.26 ± 5.77	6.29 ± 4.40	6.31 ± 4.43	0.000	0.000	0.123
	V50% (Gy)	7.02 ± 5.58	7.25 ± 5.77	7.03 ± 5.69	7.23 ± 5.77	5.24 ± 3.95	5.44 ± 3.94	0.000	0.001	0.112
	V30% (Gy)	12.88 ± 5.77	13.38 ± 5.96	12.74 ± 6.34	13.09 ± 5.96	10.78 ± 4.80	10.90 ± 4.77	0.001	0.001	0.087
	V10Gy (%)	42.48 ± 19.13	43.62 ± 18.84	40.65 ± 20.85	41.36 ± 18.84	33.87 ± 14.42	33.95 ± 14.28	0.011	0.001	0.030
	Dmean (Gy)	10.08 ± 4.48	10.53 ± 4.62	10.38 ± 4.83	10.61 ± 4.62	8.70 ± 3.95	8.76 ± 3.38	0.000	0.000	0.187
SPINAL CORD	Dmax (%)	8.33 ± 4.36	8.20 ± 4.59	7.55 ± 2.51	7.50 ± 2.50	6.98 ± 3.58	6.97 ± 4.59	0.752	0.000	0.000
	V0.35cc (Gy)	7.44 ± 4.02	7.32 ± 4.19	6.83 ± 2.29	6.75 ± 2.33	6.38 ± 3.20	6.36 ± 4.19	0.124	0.811	0.859
	V1.2cc (Gy)	6.69 ± 3.80	6.60 ± 3.94	6.34 ± 2.21	6.30 ± 2.21	5.99 ± 2.96	5.96 ± 3.94	0.150	0.943	0.925
SKIN	V0.5cc (Gy)	19.49 ± 13.15	18.40 ± 13.54	19.93 ± 14.12	19.53 ± 13.54	17.54 ± 13.81	16.93 ± 13.31	0.242	0.825	0.661
	V10cc (Gy)	15.84 ± 13.41	15.53 ± 13.74	15.69 ± 14.36	14.99 ± 13.74	13.84 ± 13.80	13.74 ± 13.44	0.000	0.000	0.004
BODY-PTV	Dmean (Gy)	1.98 ± 0.75	1.95 ± 0.70	1.98 ± 0.76	1.96 ± 0.63	1.69 ± 0.63	1.67 ± 0.62	0.000	0.000	0.010
	1Gy (%)	23.76 ± 7.56	23.71 ± 7.36	24.97 ± 7.91	24.71 ± 7.36	23.35 ± 7.12	22.88 ± 7.00	0.000	0.000	0.014
	2Gy (%)	18.59 ± 6.29	18.29 ± 6.12	18.93 ± 6.45	18.8 ± 6.12	18.02 ± 5.97	17.719 ± 5.92	0.469	0.001	0.000
	3Gy (%)	14.58 ± 5.20	14.44 ± 5.05	15.59 ± 5.46	15.5 ± 5.05	14.73 ± 5.23	14.53 ± 5.19	0.000	0.028	0.000
	4Gy (%)	12.56 ± 4.58	12.52 ± 4.47	13.49 ± 4.78	13.31 ± 4.47	12.35 ± 4.60	12.21 ± 4.59	0.013	0.810	0.010
	5Gy (%)	11.49 ± 4.17	11.46 ± 4.09	11.69 ± 4.36	11.63 ± 4.09	10.49 ± 4.10	10.38 ± 4.09	0.127	0.013	0.011
Monitor Unit	MU	1118 ± 71.91	1220 ± 94.93	1245 ± 518	1273 ± 94.93	2857 ± 587	2968 ± 5.65	0.000	0.000	0.320
Beam on time	BOT	1.86 ± 0.04	0.51 ± 0.04	2.38 ± 0.94	0.64 ± 0.19	5.92 ± 1.18	1.48 ± 0.28	0.00	0.00	0.00
Normal tissue integral dose $x10^3$Gycc		36.38± 14.78	35.83± 16.20	36.86 ± 12.98	36.04 ± 15.08	31.05± 16.40	30.69 ± 12.87	0.000	0.000	0.010

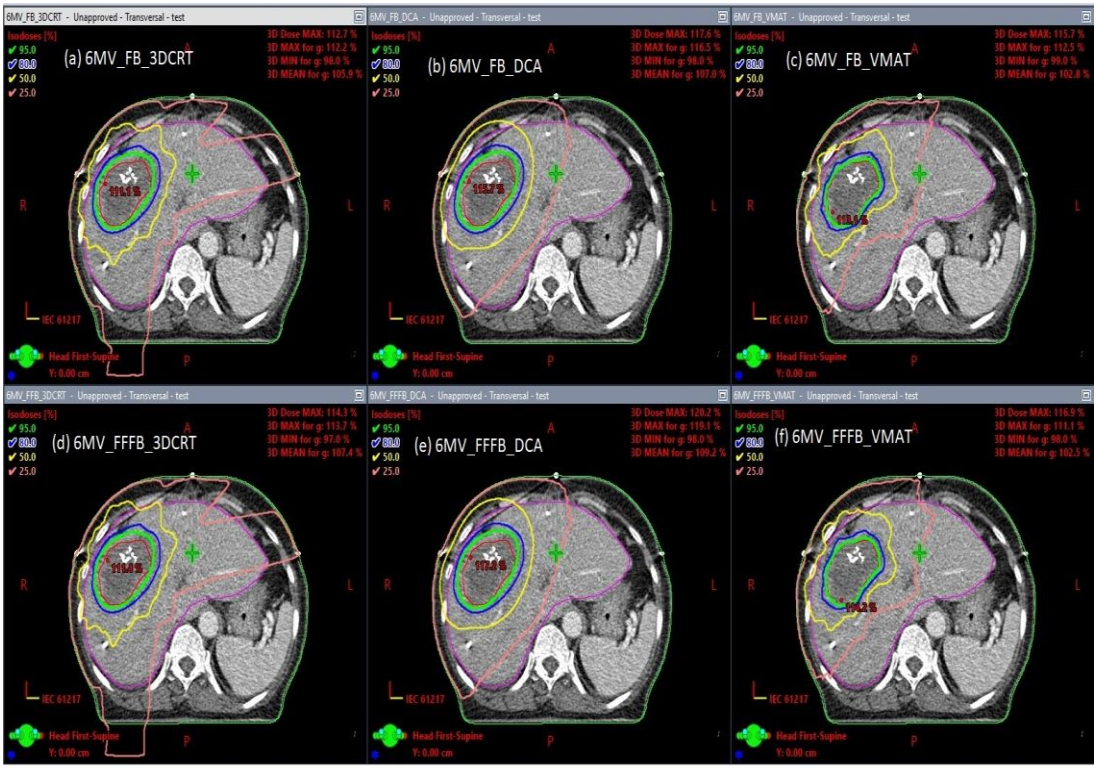

Figure 2. 6MV FB/FFFB transverse plane isodose distribution for one patient in all six plans like (a) 6MV_FB_3DCRT (b) 6MV FB_DCA (c) 6MV_FB_VMAT (d) 6MV_FFFB_ 3DCRT (e) 6MV_FFFB_DCA (f) 6MV_FFFB_ VMAT.

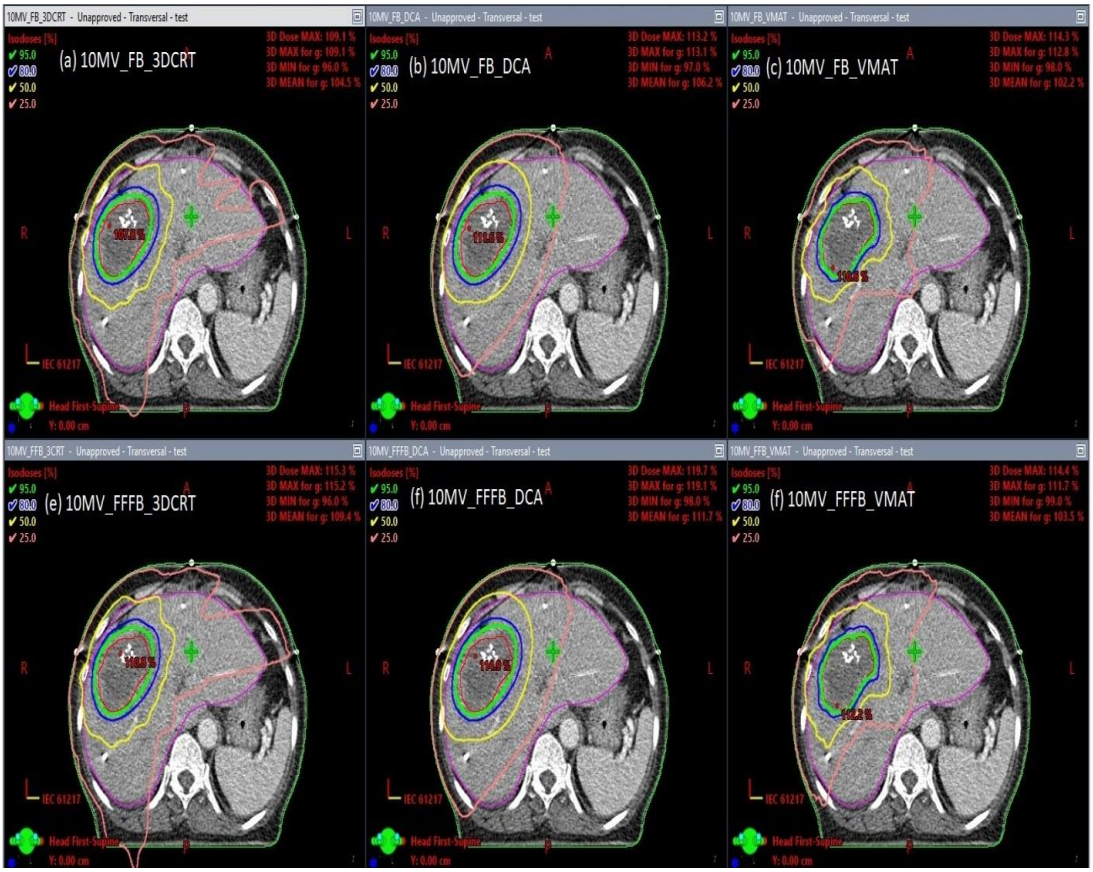

Figure 3.10MV FB/FFFB transverse plane isodose distribution for one patient in all six plans like (a) 10MV_FB_3DCRT (b) 10MV_FB_DCA (c) 10MV_FB_VMAT(d) 10MV_FFFB_3DCRT (e) 10MV_FFFB_DCA (f) 10MV_FFFB_ VMAT.

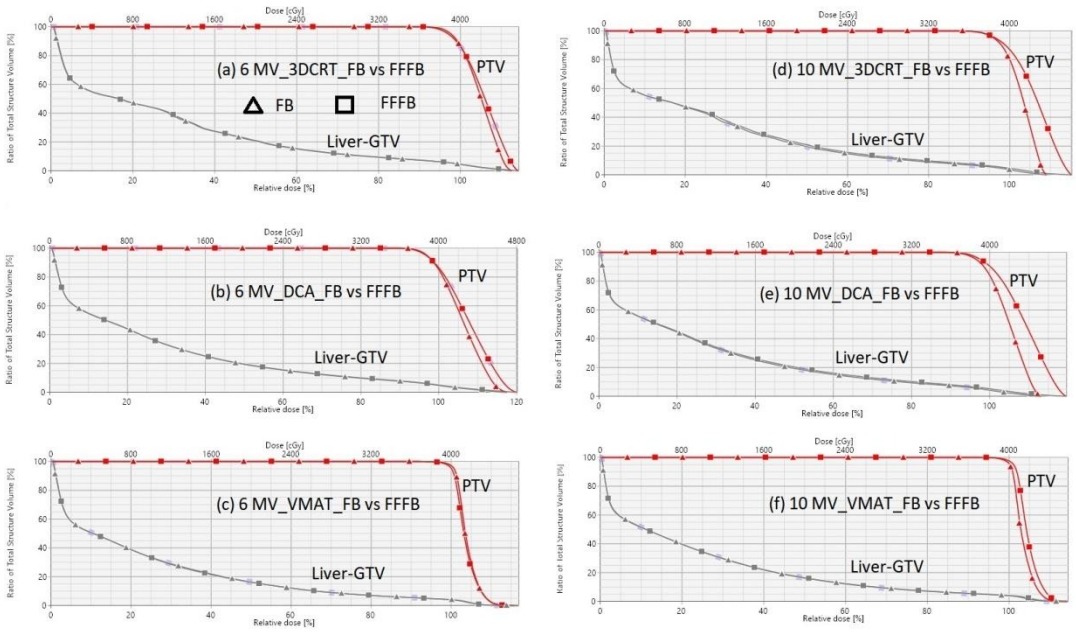

Figure 4. Dose volume histogram for PTV and Liver-GTV in all three plans like (a) 6MV_3DCRT_FB/FFFB (b) 6MV_DCA_FB/FFFB (c) 6MV_VMAT_FB/FFFB (d) 10MV_3DCRT_FB/FFFB (e) 10MV_DCA_FB/FFFB (f) 10MV_VMAT_FB/FFFB for one patient. Triangle line for FB and square for FFFB plan.

The values ofD_{700cc} of liver-GTV were 8.46 vs. 8.70 Gy (p=0.00), 8.29 vs. 8.35 (p=0.486), 6.33 vs. 6.40 Gy (p=0.126) for 6 MV 3DCRT, DCA and VMAT as compared to 6 MV FB vs. FFFB, in the case of 10MV the value were 8.09 vs. 8.44 Gy (p=0.00), 8.02 vs. 8.26 (p=0.00), 6.29 vs. 6.31 Gy (p=0.123).

The values of V_{10Gy} of liver-GTV were 43.86 vs. 44.29 % (p=0.027), 41.14 vs. 41.4 (p=0.646), 33.74 vs. 33.93 % (p=0.093) for 6 MV 3DCRT, DCA and VMAT as compared to 6 MV FB vs. FFFB, in the case of 10MV the values were 42.48 vs. 43.62 % (p=0.011), 40.65 vs. 41.36 % (p=0.001), 33.87 vs. 33.95 % (p=0.030). The dose to the spinal cord (D_{max}, $V_{0.35cc}$ and $V_{1.2cc}$)is 2-13% and body ($V_{0.5cc}$ and V_{10cc}) is about 8-10% lower in the 6 MV VMAT than 6 MV 3DCRT and 6 MV DCA plans.In the case of 10 MV the dose to spinal cord (D_{max}, $V_{0.35cc}$ and $V_{1.2cc}$) is 6-16% and body ($V_{0.5cc}$ and V_{10cc}) is about 10-12% lower in the 10 MV VMAT than 10 MV 3DCRT and 10 MV DCA plans.

The VMAT plan reduces the NTID, D_{mean}, and the effects of 1Gy to 5Gy in the non-tumor volume (body-PTV). The D_{mean} values were 2.05 vs. 2.03Gy (p=0.028), 2.03 vs. 2.01 Gy (p=0.133), 1.76 vs. 1.74 Gy (p=0.002) for 3DCRT, DCA and VMAT plans as compared to 6MV FB and FFFB. In 10 MV, the values were 1.98 vs. 1.95 Gy (p=0.00), 1.98 vs. 1.96 Gy(p=0.00) and 1.69 vs. 1.67 Gy (p=0.010)for 3DCRT, DCA and VMAT plans as compared to 10 MV FB vs. FFFB.

From the figure5, the increased MU in FFFB is due to the non-uniform beam profile of FFFB. The 6 MV FFFB plan needs higher MU in 3DCRT (1286 vs. 1405 MU, p= 0.00), DCA (1369 vs. 1576 MU, p = 0.068) and 3231 vs. 3368 MU, p = 0.003 for VMAT as compared to FB. In the case of 10 MV FFFB plan needs higher MU in 3DCRT (1118 vs. 1220 MU, p = 0.00), DCA (1245 vs. 1273 MU, p = 0.667) and 2857 vs. 2968 MU, p = 0.791 for VMAT plans as compared to FB. From figure 6, the present study the BOT of FFFB reduced compared to FB in all techniques.The values of BOT for 3DCRT (2.14 vs. 1.0 min for 6 MV and 1.86 vs. 0.51 min for 10 MV), DCA (2.74 vs. 1.22 min for 6 MV and 2.38 vs. 0.64 min for 10 MV), VMAT (6.46 vs. 2.81 min for 6 MV and 5.92 vs. 1.48 min for 10 MV) is 55-75 % lesser in FFFB.From figure 7 to 9, as the dose increases, the non –volume decreases gradually in FB and FFFB.

Various CI formulas were used to find the extent of planned isodose distribution and to confirm whether prescription isodose covers the size and shape of the target. The present study VMAT plan gives highly conformal techniques compared to 3DCRT and DCA. The mean CI_{RTOG} value is 1.43 for 3DCRT, 1.39 in DCA, and 1.19 for VMAT plans. The Saint-Anne, Lariboisiere, and Tenon group (SALT) defined the CI to calculate the reference prescription isodose volume in the target volume. The ideal value is 1. In our study, the entire plan the CI_{SALT} is 1. To find the prescription isodose volume in healthy tissue, Lomax and Scheib et al. proposed the CI, called healthy tissue conformity index, and the nominal value is greater than 0.6. The CI of Lomax and Scheib is better in VMAT ($CI \geq 0.83$) as compared to 3DCRT and DCA ($CI \geq 0.7$). The nominal value of HI_{RTOG} is two, and for all the techniques, the HI_{RTOG} value is < 1.2. Similarly, the ideal value of HI_{ICRU} is zero, and in all the plans, the HI_{ICRU} is less than 0.12.

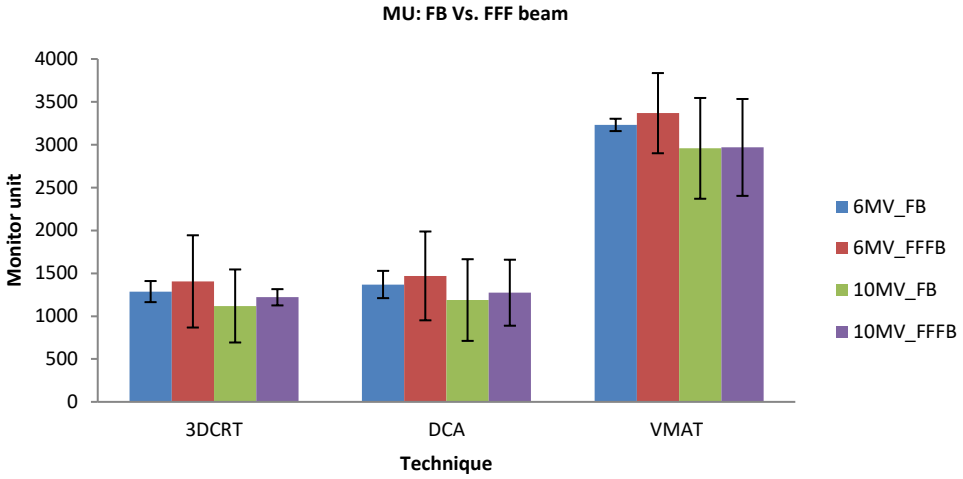

Figure 5. Monitor unit comparison for 6MV and 10 MV FB/FFFB for 3DCRT, DCA, and VMAT techniques.

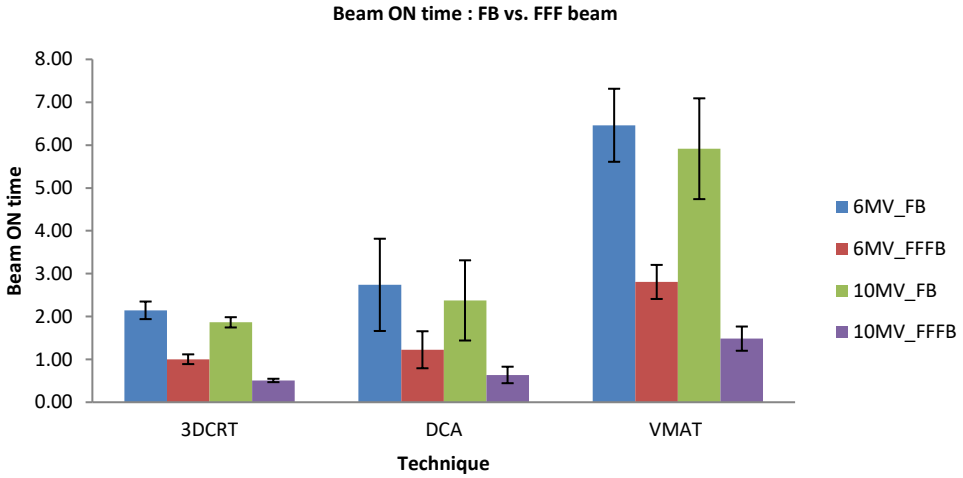

Figure 6. Beam on time comparison for 6MV and 10 MV FB/FFFB for 3DCRT, DCA, and VMAT techniques.

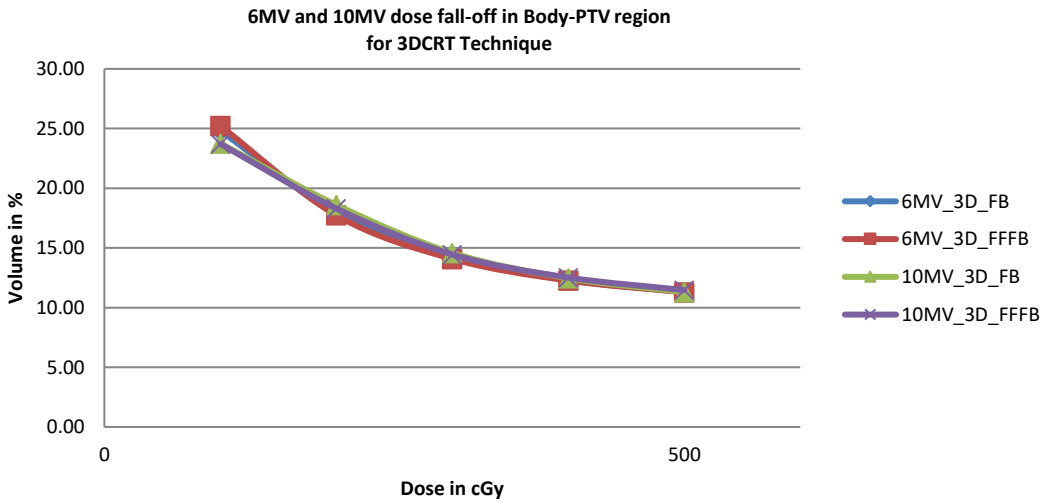

Figure 7. 6MV and 10MV dose fall-off in Body-PTV regionfor 3DCRT Technique.

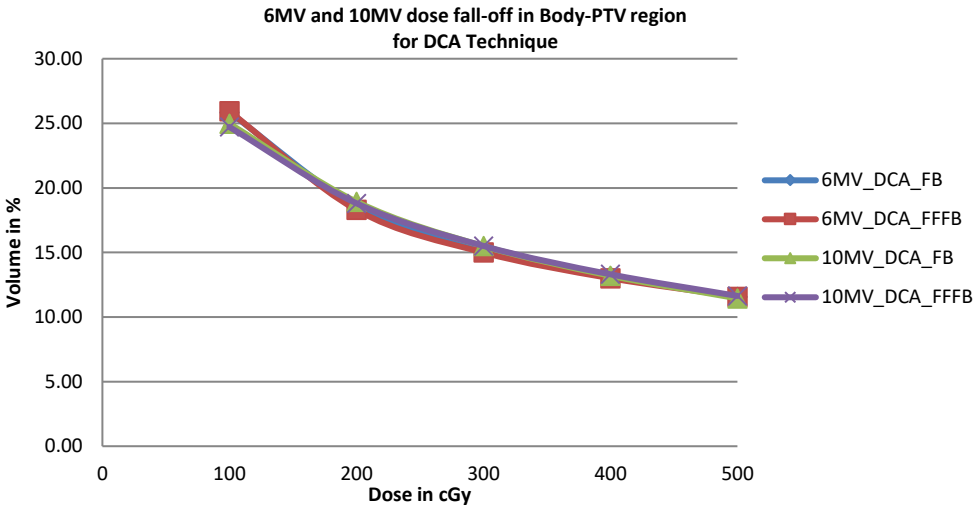

Figure 8. 6MV and 10MV dose fall-off in Body-PTV region for DCA Technique.

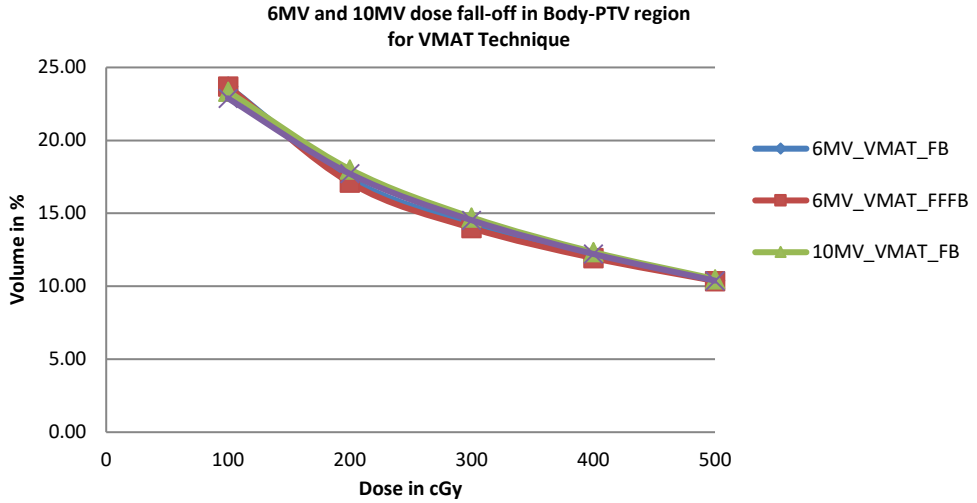

Figure 9. 6MV and 10MV dose fall-off in Body-PTV region for VMAT Technique.

The VMAT plan gives better, CN value as compared to 3DCRT and DCA plan. The CN is 0.65 vs. 0.71 (p= 0.00), 0.68 vs. 0.67, (p = 0.880) and 0.79 vs. 0.82, p = 0.015 for 3DCRT, DCA and VMAT plans ascompared to 6 MV FB to 6 MV FFFB. In the case of 10MV, the CN is 0.79 vs. 0.69 (p= 0.072), 0.70 vs. 0.74 (p = 0.71) and 0.85 vs. 0.82 (p = 0.776) for VMAT plans s to 10 MV FB to 10 MV FFFB.

The dose gradient outside the PTV (body-PTV region) is expressed in terms of GI_{high} and GI_{low}. The $GI_{high}$is defined as the volume of 50% prescription isodose volume (PIV) divided by 90% PIV and the $GI_{low}$is defined as the volume of25% PIV divided by 50% PIV.In our study, the GI_{PAD} is less in VMAT plans the value is < 3.3, other plans like 3DCRT and DCA are > 3.9. Similarly, the HGI and LGI value reduces in VMAT plans. The HGI value is 2.77 vs. 2.87 (p=0.006), 2.68 vs. 2.87 (p=0.135) and 2.59 vs. 2.61 (p=0.010) for 6MV, in the case of 10 MV, the value is 2.72 vs. 2.74 (p=0.00), 2.68 vs. 2.7 (p=0.00), and 2.54 vs. 2.56 (p=0.076) for 3DCRT, DCA and VMAT as compared to FB vs. FFFB. Similarly, the 6 MV LGI value is 4.45 vs. 4.48 (p=0.041), 3.31 vs. 3.44 (p=0.266) and 3.45 vs. 3.50 (p=0.037), in the case of 10 MV, the LGI value is 4.17 vs. 4.24(p=0.267), 3.19 vs. 3.20 (p=0.144) and 3.27 vs. 3.29 (p=0.177) for 3DCRT, DCA and VMAT respectively.

The CGIg is 78.3 vs. 76.15 (p = 0.132), 84.77 vs. 82.28 (p = 0.115) and 86.19 vs. 84.77 (p = 0.000) 3DCRT, DCA and VMAT as compared to 6 MV FB to 6 MV FFFB. The CGIg is 86.51 vs. 84.05 (p = 0.002), 87.87 vs. 86.9 (p = 0.00), and 89.61 vs. 89.44 (p = 0.503) for 3DCRT, DCA and VMAT plans as compared to 10 MV FB to 10 MV FFFB. The nominal value of DGI of 100, 90,80 and 70 corresponds to 3mm,4mm,5mm and 6mm dose gradient. The VMAT plan produces better DGI as compared to 3DCRT and DCA. The dose gradient value were 5mm, 4.5mm, 4mm

for 6MV 3DCRT, DCA and VMAT, in the case of 10 MV the value were 4.5mm, 4mm and 3mm respectively.

The low dose spillage in normal tissue in terms of $R_{50\%}$ and D_{2cm} were reduced in VMAT than 3DCRT and DCA. The RTOG 0813 protocol nominal value for minor deviation for $R_{50\%}$is 3.3 to 4.0, and D_{2cm} is 70-89 for the PTV volume of 95cc. The $R_{50\%}$ values were 4.03 vs.4.25 (p=0.006), 4.23 vs. 4.32 (0.286) and 3.38 vs. 3.41 (p=0.046) for 3DCRT, DCA and VMAT as compared to 6MV FB and FFFB, in the case of 10 MV $R_{50\%}$ values were 3.85 vs.4.15 (p=0.000), 4.06 vs. 4.29 (0.000) and 3.37 vs. 3.39 (p=0.270). The D_{2cm} values were 70.05 vs.70.43 (p=0.607), 72.53 vs. 73.04 (0.504) and 59.68 vs. 60.36 (p=0.007) for 3DCRT, DCA and VMAT as compared to 6 MV FB and FFFB, in the case of 10 MV $R_{50\%}$ values were 68.78 vs.71.12 (p=0.002), 70.46 vs. 72.92 (0.000) and 58.73 vs. 59.76 (p=0.503).

Discussion

SBRT plays a vital role in all the anatomical sites due to the recent advances in technological innovation to deliver the high dose in a short duration. Clinically controlling toxicities and reducing the dose to OAR's, VMAT is more appropriate due to fluence being modified [31]. However, DCA calculation is simple and lower MU to deliver the plan than VMAT. VMAT helps treat multiple target lesions simultaneously in our present study IMRT planning was not chosen, because IMRT plans have certain disadvantages, like higher delivery MU, longer BOT and increased geometric uncertainties inpatient position [32]. In the present study, the PTV coverage in $D_{98\%}$and $D_{95\%}$ region is best in VMAT plan. Further VMAT plan spare the liver-GTV, reduced the BOT, highly conformal plan, and reduced the normal tissue dose in terms of lower GI, HGI, LGI, D_{2cm}, $R_{50\%}$, NTID and low dose volume of 1Gy-5Gy in normal tissue as compared to 3DCRT and DCA.

Several studies [33-35] reported that the leaf margin of 0 to 1 mm in liver SBRT cases gives optimal coverage and OAR's sparing as compared to > 2 mm leaf margin. The leaf margin around PTV in our study is 1 mm, the NTID of 6 MV FFFB of all the techniques, the value is 1 % less than 6 MV FB. In 10 MV FFFB, the NTID is 1.5 %, 1 % and 1.2 % lesser in 3DCRT, DCA and VMAT plans compared to 10 MV FB. D'Souza WD et al.[30] reported that reducing the beam margin and using higher energies will reduce the NTID significantly. The present study, the 10 MV FFFB (30.69 x 10^3Gy-cc) VMAT plan produces lesser NTID as compared 6 MV FFFB (31.98x10^3Gy- cc) VMAT plan.

Laure Vieillevigne et al.[36] compared the PTV volume versus different techniques using the FFF beam. The study recommends that the target volume <20 cc and >50 to 100 cc is suitable for DCA and VMAT techniques, respectively. The volume between 20 to 50 cc is suitable for DCA or VMAT. Further, the use of 6 MV or 10 MV FFF beam in DCA and VMAT technique needs 2% and 1.4 to 4% higher MU required as compared to FB. However, the FFF beam reduced the BOT by 54-74%, depending upon the treatment technique and beam energy. In our study, the average PTV volume is 93 cc, the PTV coverage is better in the FFFB VMAT technique than DCA and 3DCRT. The plan optimized with FFF needs 9%, 7%, and 4% more MU required for the 3DCRT, DCA, and VMAT plan, respectively. Recently Subramanian SB et al. [37] reported that the PTV volume of 75 cc using 10 MV FFF beam in combination with VMAT technique produces the better CI, HI, and GI. The values were 1.18,1.13 and 3.29 in re-irradiation of spine SBRT cases. Kumar R et al.[38] reported that the one-year local control, overall survival, and progression-free survival in SBRT liver case, the values were 95%, 60%, and 53.4%, respectively. The PTV volume is 275 cc, and the dose prescription is 48Gy delivered in 6 fractions using 10 MV FFFF VMAT.

Plato C. Lee et al. [39] reported that the fluence-weighted photon energy at central axis for 6 MV FB is 1.93MeV, and 6 MV FFFB is 1.36 MeV. This reduction of average energy will reduce the integral dose in the body-PTV region will be noted in our study. D'Souza WD et al. [30] defined the NTID, i.e the volume integral of the dose deposited in a patient is equal to mean dose multiplied by volume irradiated to any dose. In all techniques, the FFFB plan reduced the body - PTV means dose and a low dose of 1Gy to 5 Gy volume contributions in non-target volume is lesser than FB.

D_{2cm} and $R_{50\%}$ parameters [40] were used in lung SBRT patients to control the low dose volume in non PTV region. Lim DH et al. [41] reported that the use of non-coplanar beams fields produce lower $R_{50\%}$ than co-planner fields. The present study using co-planner beams, VMAT plans the value is lower ($R_{50\%}$: <3.41, D_{2cm} :< 60.36%) as compared to 3DCRT ($R_{50\%}$: < 4.25, D_{2cm} : < 70.43%) and DCA plan ($R_{50\%}$: < 4.32 , D_{2cm} : <73.04%).

Bignardi M et al. [42] reported that the SBRT for metastases to abdominal lymph nodes cases, the treatment time is reduced in volumetric arc therapy (3.7min) as compared to IMRT (10.6min) and 3DCRT (6.3min). Prendergast BM et al. [43] demonstrated that using an FFFB in lung and liver SBRT cases reduces the treatment delivery time by 50% compared to conventional FB. The present study the BOT is reduces an average of 53%, 55%, 57 % in 6 MV 3DCRT, DCA and VMAT and an average of 73% in 10 MV FFFB of all techniques as compared to FB.

Conclusion

In our study, the FFFB VMAT plan generates a highly conformal plan and spares the normal liver as compared to DCA and 3DCRT in liver SBRT cases. VMAT, in combination with FFFB, is suitable for SBRT liver lesions will help faster the treatment delivery and reduce the dose discrepancies effect of moving targets. Further FFFB VMAT will be more useful for re-irradiation cases to control the dose to nearby OAR's.

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