

A dosimetric study on flattening filter free beam impact of multi-criterial optimization in hepatocellular carcinoma stereotactic body radiotherapy using Monte Carlo algorithm

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ABSTRACT

► Original article

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Received: November 2024

Final revised: May 2025

Accepted: June 2025

Int. J. Radiat. Res., January 2026;
24(1): 83-90

DOI: 10.61186/ijrr.24.1.13

Keywords: Multi-criterial optimization, standard direct machine optimization, stereotactic body radiotherapy, Monte Carlo, flattening filter free.

Background: Studying the influence of multi-criterial optimization (MCO) on dosimetry in stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma patients, utilizing Flattening Filter Free (FFF) photon energies through Monte Carlo (MC) algorithm. **Materials and Methods:** Hepatocellular carcinoma SBRT plans were generated at a prescribed dose of 35 Gy in 5 fractions, with Standard Direct Machine Optimization (SDMO) and multi-criteria optimization for two energies of 6 and 10 MV FFF using MC algorithm in Monaco Planning Station. These plans were compared within and across the groups based on various plan quality metrics such as target coverage, Conformity Index (CI), Homogeneity Index (HI), Monitor Unit (MU) and Organ at Risk (OAR) dose. **Results:** Using MCO technique, plans with comparable target outcome measures and slightly improved OAR sparing are produced, with the consequence of increased MU for both energies ($p=0.030$ & $p=0.002$ respectively). In the case of 6 MV FFF plans using MCO, the degree of CI within the target showed a statistical significance ($p=0.013$) and provided plans with better OAR sparing and for 10 MV FFF energy showed no observable statistical significance for any target outcome measures such as CI, HI or V95%. **Conclusion:** With efficient treatment planning time, MCO is a valuable tool for providing optimal SBRT plans, however it results in longer treatment times due to increase in MU. Out of the SBRT plans generated the MCO plan using 6 MV FFF energy shows little superiority than others, with a better balance in target coverage and OAR sparing.

INTRODUCTION

Liver carcinoma being the third common leading cause of death globally with hepatocellular carcinoma accounting for 75% to 85% ⁽¹⁻³⁾. External beam radiation therapy is a prominent treatment mode for such types of carcinomas by utilizing high energy radiation, through various planning techniques such as 3D-Conformal radiotherapy, intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic radiotherapy, stereotactic body radiation therapy (SBRT) etc. ^(4, 5). Among these SBRT, which is typically delivered over a span of 5 fraction or less, is an emerging and advanced form of radiotherapy technique, particularly suited for liver cancer patients who are not a good candidate for surgery ⁽⁶⁾. Owing to the high dose per treatment fraction required to deliver the prescribed tumor dose with minimizing radiation-induced adverse effects, specialized planning

approaches must be employed for these techniques. Flattening Filter Free (FFF) photon beam is the first preference for such planning technique due to its advantages such as, low head scatter, higher dose rate, lower treatment time over Flattening Filter (FF) beam ⁽⁷⁻⁹⁾.

The effectiveness of an SBRT plan largely dependent on the planner's expertise, the planning technique used and the algorithm applied for dose computation ⁽¹⁰⁾. Various vendors offer different dose calculation algorithms, with the Monte Carlo (MC) method being widely regarded as one of the most accurate and reliable for dose estimation and assessment ^(11, 12). Recent advancements in treatment planning have significantly improved optimization and computation processes, enabling automated workflows and greater precision in dose estimation. Multi-Criteria Optimization (MCO) is one such innovation in inverse planning, which involves a cost function that prompts the optimizer to prioritize the

flagged constraint to reduce the isoconstraint beyond the specified limit, while still maintaining the target doses. In other terms MCO which is also known as Multiple objective optimizations, is an advanced approach that considers multiple objectives simultaneously to get an optimal plan in Radiotherapy. One of the notable advantages of this optimization process facilitated by MCO is the capability to optimize for dose homogeneity within the PTV. This allows users to mitigate hotspots and enhance minimum dose coverage. Several studies have demonstrated that MCO is an efficient treatment planning tool for cases where no single optimal solution is available, ensuring dosimetric accuracy and a shorter treatment planning time⁽¹³⁻¹⁸⁾. MCO uses anatomically unique approaches for each patient. Several research investigations have been carried out regarding the quality of plans, as well as the time taken for planning and delivery, using MCO IMRT for cases involving the head, neck, and pelvic regions⁽¹⁹⁻²¹⁾. Additionally, further researches have examined VMAT with MCO to evaluate plan quality, efficiency, and delivery⁽²²⁻²⁷⁾.

Based on the current understanding of MCO for radiotherapy treatment planning, it has been demonstrated to be an efficient and promising tool. MCO facilitates the generation of high-quality treatment plans while requiring fewer resources and significantly reducing planning time. While numerous studies have explored the application of MCO in VMAT and IMRT for various tumor sites, there is still a scarcity of literature specifically investigating its use in SBRT for hepatocellular carcinoma. The primary objective of this study is to evaluate the Dosimetric performance of our proposed MCO-based SBRT planning method. This evaluation was conducted by comparing the Dosimetric parameters of clinically deliverable MCO-generated plans with those created using the Standard Direct Machine Optimization (SDMO) approach. To ensure a robust comparison, plan quality metrics were analyzed both within individual groups and across groups. All treatment plans were generated using the Monaco treatment planning system, employing the MC dose calculation algorithm in constrained optimization mode. The analysis included two nominal photon energies 6 MV and 10 MV both using FFF beams, which are particularly advantageous in SBRT due to their high dose rate and sharper dose fall-off. This study aims to assess the potential benefits and clinical applicability of incorporating MCO into SBRT treatment planning for hepatocellular carcinoma, with a focus on determining whether MCO can enhance plan quality and efficiency when using FFF beams.

MATERIALS AND METHODS

This is a retrospective observational study in

which fourteen patients, of any gender, who had been diagnosed with hepatocellular carcinoma and matched our study requirements were chosen from Kasturba Medical College's patient records (Treated between 2022-2023 Years). The whole study was carried out with the approval of Institutional Research Committee, Manipal Academy of Higher Education [Ref: MCHP-Mpl/IRC/PG/2023/222] and Approved by Institutional Ethics Committee - 2 (Student Research), Kasturba Medical College and Kasturba Hospital [IEC2: 227/2024]. Metastatic cases and pediatric cases were excluded in selecting subjects. Sample size (n) is calculated using the equation 1⁽²⁸⁾:

$$n = [(Z_{(1-a/2)} + Z_{(1-b)}) s / d]^2 \quad (1)$$

Where; $Z_{(1-a/2)} = 1.96$ [with 95% CI], $Z_{(1-b)} = 0.842$, [Power], $d = 20\%$ [Margin Error], $s = 0.0001$ [Standard Deviation]

During the simulation process, the patient is positioned and immobilized on the Conventional Tomography (CT) simulator couch with the head-first supine position and using a thermoplastic mould (ORFIT- Belgium) that is customized for the tumor site. The Philips Big Bore CT Scanner (Netherland) is used to acquire CT images of every patient, with a slice thickness of 3 mm^(29, 30). These reconstructed images were then transmitted to the Monaco treatment planning system (Version 5.11- Stockholm, Sweden) for the reconstruction and delineation of target and OARs.

Once the raw images were imported in the planning station Radiation oncologists define Gross Tumor Volume (GTV), Clinical Target Volume (CTV), and Planning Target Volume (PTV) for each patient in accordance with recommendations from Radiation Therapy Oncology Group (RTOG) and Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines. The observable size and location of the tumor volume, along with associated lymph nodes or metastases, essentially constitute the GTV. A CTV structure, which is denoted by extending the margin of the GTV, shows the tumor as well as any other tissue that may be suspected of having a malignancy were also registered. A setup margin, generally about 5-7mm, that accounts for setup errors are included in the PTV alongside the CTV⁽³¹⁾. The prescription for maximum dose tolerances is also stated and labeled for the OARs, which include organs like the stomach, duodenum, esophagus, heart, kidney, lungs, spinal cord, etc.

The Versa HD™ linear accelerator from Elekta (Elekta, Crawley, United Kingdom) with an Agility™ multi-leaf collimator (160 leaves with a spatial resolution at the isocentre of 5 mm) is used in our clinic to carry out SBRT treatments. SBRT plans (using full or half arc) were generated for 14 patients using nominal energies of 6 and 10 MV photon beams in FFF mode as shown in figure 1. For each patient,

the PTV was prescribed at a dose of 35 Gy in 5 fractions (7 Gy per fraction). The primary objective of planning is to achieve 95% of the target volume with 95% of the prescribed dose. The MC algorithm is used in constrained mode to optimize plans to achieve this goal, after suitable constraints are provided. For each patient, four plans were created in total: two using 6 MV FFF beams (one with standard iterative optimization and one with multicriteria optimization (MCO)), and two using 10 MV FFF beams under the same conditions. These plans were then compared within and across groups to assess the effects of MCO on SBRT plans for liver cancer patients.

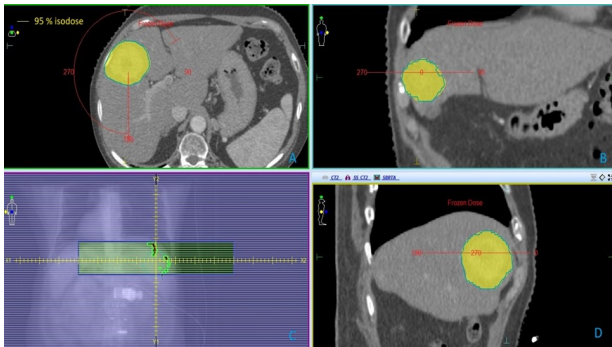


Figure 1. SBRT plan view; **A** axial view, **B** Coronal view, **C** beams Eye view, **D** Sagittal view.

SBRT liver plans were evaluated using several Dosimetric quality metrics, such as PTV coverage, Homogeneity Index (HI), Conformity Index (CI), Monitor Unit (MU), and specific OAR dose constraints. The objective is to identify a treatment plan that ensures adequate target coverage (95% of the volume receiving 95% of the prescribed dose) while adhering to established dose limits for Oars. This approach aims to maximize radiation delivery to the target while minimizing exposure to nearby critical structures and healthy tissues.

Where, HI is a metric used in radiotherapy treatment planning that quantifies the degree of homogeneity within the target volume and is calculated by taking the ratio of dose received in 5% of the target volume (D5%) to the dose received in 95% of the target volume (D95%) calculated by using equation 2 ⁽³²⁾.

$$HI = \frac{D5\%}{D95\%} \quad (2)$$

The optimum value of HI is unity, denoting perfect homogeneity. The plan becomes less homogeneous when the HI value rises over 1. CI is an index proposed by RTOG to know the extent of conformation of the dose to the tumor in the treatment plan. It is calculated by equation 3 as the ratio of the volume covered by the reference isodose (VRI) to the total target volume (TV) ⁽³³⁾.

$$CI = \frac{VRI}{TV} \quad (3)$$

The ideal CI value is one; the value below one indicates that the target volume is partially

irradiated, and the value above one indicates that the volume of tissue receiving the prescribed dose is greater than the target volume. The term MU refers to the measure of the beam ON time for linear accelerator. It indicates the total amount of radiation delivered during exposure. It aids in finding the optimal plan which delivers the dose with a shorter duration. Generally, 1 cGy is considered as 1 MU at the isocentre.

The DVH parameters of the PTV and OARs were analyzed using statistical methods. Specifically, the normality of the data distribution was assessed via the Shapiro-Wilk test, to evaluate the differences between the groups. The significance of the parameter under consideration is assessed using the paired t-test if it is found to follow a normal distribution; if not, the Wilcoxon signed-rank test is employed. This methodology is subject to the same assumptions as a paired sample t-test. This research estimates the p-value, which is used to determine whether any statistical significance exists. As seen by the p-value of less than 0.05 when comparing the plans, there is less than a 5% chance of getting a result comparable to the observed one if the null hypothesis is true, that means there is a significant difference between the groups can be proclaimed. If the measured p-value exceeds 0.05, then there is no statistically significant difference between the tested groups.

RESULTS

A database of treatment plans was established for all the 14 patients, (table 1) with a mean target volume of 292.69 ± 335.57 cc. The dosimetric quality of the plans that utilized SDMO and those that used MCO were evaluated using multiple conformity metrics. Target coverage, indicated by V95%, MU, CI, HI and dosage readings in certain significant OARs are among the parameters taken into consideration as shown in table 2. The following outcomes were obtained from these comparisons in terms of their p-values:

Table 1. Patient characteristics.

Variables	Patients with HCC
Age (mean $\pm$ SD)	54.3 $\pm$ 9.3
Gender (female/male, %)	21.4/78.6
Body mass index (kg/m ²)	27.1 $\pm$ 4.2
Total bilirubin (mg/dl)	2.31 $\pm$ 2.17
Diabetes Mellitus (%)	33
Hypertension (%)	63
Smoking (%)	68
Alcohol (%)	47
Tumor stage (I/II/III, %)	21.4/28.5/50.1
Albumin (g/dl)	3.1 $\pm$ 0.6

The comparison of SDMO and MCO plans employing 6 MV FFF energy revealed statistical significance in terms of CI and MU, with p-values of 0.013 and 0.030, respectively. For MCO plans, the

mean and standard deviation of MU is 2338.75 ± 685 , while for plans with SDMO it is 2115.07 ± 503.54 . Furthermore, no statistically significant results were observed for measures such as the percentage volume receiving 95% of the prescribed dose (V95%) or the maximum dose (Dmax) in cGy delivered to the target volume as shown in table 2 below. It has been discovered that the degree of conformity of dose to the target volume for MCO plans increases, with a mean value of 1.32 ± 0.20 . The variation in CI within the target volume is plotted in figure 2. It also turned out that plans with MCO utilize a greater MU to deliver the treatment, which pointed to a longer beam ON time, as shown in figure 3. The research revealed significance for a few OAR parameters, which can be inferred from table 3, suggesting that MCO plans could lead to an improved sparing of specific OARs. Several OAR parameters were found to have significantly decreased in MCO plans: maximum dose (Dmax) in cGy received by bowel loops, stomach, left kidney, right lung, and left lung; mean dose (Dmean) in cGy received by heart, right kidney, left kidney, and left lung; and percentage volume receiving 10 Gy (V10) of heart and right kidney. The variation in mean dose received by right kidney is plotted in figure 4.

Table 2. Relative target Dose distribution with monitor units for Multi criterial optimization and Direct Machine Optimization.

PARAMETER	6 MV FFF (Mean $\pm$ SD)		10 MV FFF (Mean $\pm$ SD)		p-eval			
	DMO	MCO	DMO	MCO	6 DMO/ MCO	10 DMO/ MCO	6/10 DMO	6/10 MCO
V95% (%)	99.2 $\pm$ 0.95	99 $\pm$ 1.01	99.2 $\pm$ 0.91	98.5 $\pm$ 1.56	0.230	0.083	0.836	0.196
Dmax (cGy)	3866.3 $\pm$ 224.2	3863.1 $\pm$ 232.9	3877.88 $\pm$ 227.1	3873.52 $\pm$ 227.1	0.700	0.442	0.903	0.761
CI	1.44 $\pm$ 0.20	1.32 $\pm$ 0.20	1.45 $\pm$ 0.23	1.30 $\pm$ 0.24	0.013	0.108	0.497	0.383
HI	1.07 $\pm$ 0.05	1.08 $\pm$ 0.05	1.07 $\pm$ 0.06	1.08 $\pm$ 0.05	0.072	0.168	0.282	0.091
MU	2115.07 $\pm$ 503.54	2338.75 $\pm$ 685	2119.88 $\pm$ 487.6	2365.41 $\pm$ 651.7	0.030	0.002	0.502	0.326

*DMO: Direct Machine optimization, MCO: Multi-Criterial Optimization, FFF: Flattening Filter Free (average target volume 292.69 $\pm$ 335.57 cc).

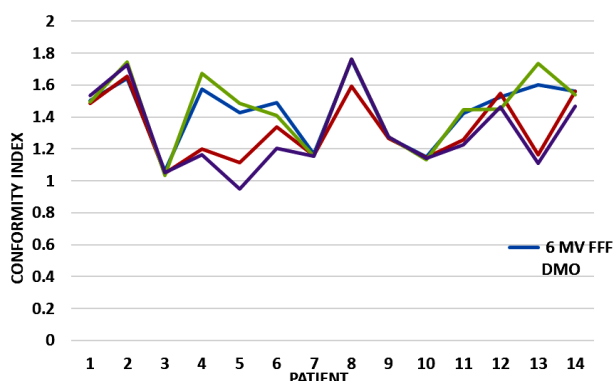


Figure 2. Variation in conformity index of the target volume with DMO and MCO (MCO: Multi-Criterial Optimization, DMO: Direct Machine Optimization, FFF: Flattening Filter Free).

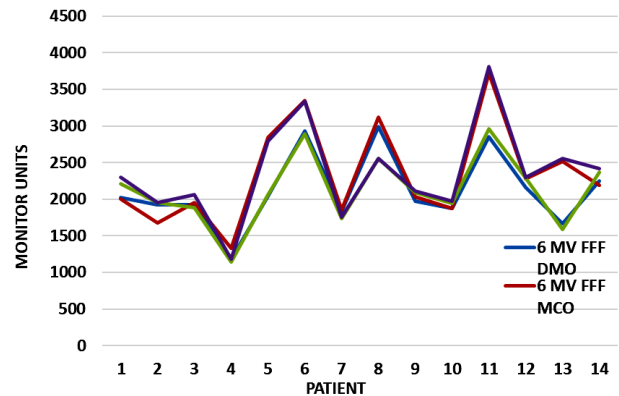


Figure 3. Monitor units with MCO and DMO for 6MV FFF (MCO: Multi-Criterial Optimization, DMO: Direct Machine Optimization, FFF: Flattening Filter Free).

Table 3. Dosimetric comparison of OARs with MCO for 6 and 10 MV FF.

OARs (cc) (Mean $\pm$ SD)	Parameter	6 MV FFF (Mean $\pm$ SD) cc		10 MV FFF (Mean $\pm$ SD) cc	
		DMO	MCO	DMO	MCO
Liver-GTV 1177.0 $\pm$ 291.6	D50%(cGy)	1273.9 $\pm$ 61.4	1147.0 $\pm$ 59.4	1286.1 $\pm$ 639.5	1134.0 $\pm$ 596.9
Stomach 218.5 $\pm$ 90.4	Dmax(cGy)	2226.1 $\pm$ 783.5	2129.9 $\pm$ 37.0	2297.6 $\pm$ 789.5	2098.9 $\pm$ 716
	Dmean (cGy)	784.1 $\pm$ 406.6	769.4 $\pm$ 399.2	793.7 $\pm$ 414.8	766.8 $\pm$ 406.4
Duodenum 57.9 $\pm$ 18.2	Dmax(cGy)	2287.4 $\pm$ 945.5	2213.0 $\pm$ 892.8	2312.0 $\pm$ 975.8	2168.5 $\pm$ 867.5
	Dmean(cGy)	618.0 $\pm$ 423.5	589.1 $\pm$ 430.66	638.9 $\pm$ 435.8	581.6 $\pm$ 432.7
Esophagus 23.2 $\pm$ 9.4	Dmax(cGy)	1511.2 $\pm$ 962.9	1498.7 $\pm$ 887.0	1536.9 $\pm$ 962.2	1507.5 $\pm$ 857.0
	Dmean(cGy)	506.8 $\pm$ 379.9	486.2 $\pm$ 6.5	520.4 $\pm$ 39.9	483.8 $\pm$ 397.6
Skin 2094.7 $\pm$ 803.5	Dmax(cGy)	2150.9 $\pm$ 610.0	2485.9 $\pm$ 572.7	2410.4 $\pm$ 637.4	2322.6 $\pm$ 588.3
Spinal Cord 28.4 $\pm$ 10.1	Dmax(cGy)	1165.3 $\pm$ 593.9	1034.1 $\pm$ 517.9	1160.3 $\pm$ 604.1	1015.1 $\pm$ 608.3
Bowel Loops 779.1 $\pm$ 563.1	Dmax(cGy)	2460.6 $\pm$ 1071.1	2416.9 $\pm$ 1064.2	2514.2 $\pm$ 1009.0	2372.6 $\pm$ 1067.7
	Dmax(cGy)	1595.8 $\pm$ 1230.2	1528.7 $\pm$ 1216.1	1575.4 $\pm$ 1234.9	1499.2 $\pm$ 1197.9
	Dmean(cGy)	225.3 $\pm$ 210.4	214.1 $\pm$ 204.9	222.6 $\pm$ 215.4	207.3 $\pm$ 7.7
	V10(%)	5.83 $\pm$ 8.85	5.18 $\pm$ 8.20	5.69 $\pm$ 8.46	5.16 $\pm$ 8.22
Heart 631.0 $\pm$ 138.4	V20(%)	0.69 $\pm$ 1.22	0.61 $\pm$ 1.47	0.74 $\pm$ 1.27	0.64 $\pm$ 1.25
	Dmax(cGy)	2216.8 $\pm$ 1080.7	2142.6 $\pm$ 119.7	2229.3 $\pm$ 1062.8	2158.4 $\pm$ 1087.1
	Dmean(cGy)	704.3 $\pm$ 478.3	632.1 $\pm$ 433.7	716.0 $\pm$ 491.8	624.7 $\pm$ 433.0
	V10(%)	27.7 $\pm$ 23.8	24.3 $\pm$ 22.8	28.3 $\pm$ 24.2	24.4 $\pm$ 22.5
Right Kidney 148.8 $\pm$ 34.8	Dmax(cGy)	799.4 $\pm$ 569.5	686.1 $\pm$ 450.0	810.6 $\pm$ 551.0	719.7 $\pm$ 476.0
	Dmean(cGy)	319.6 $\pm$ 311.3	282.7 $\pm$ 263.6	321.8 $\pm$ 302.4	285.7 $\pm$ 269.4
	V10(%)	7.43 $\pm$ 14.84	3.81 $\pm$ 9.65	7.85 $\pm$ 15.34	3.96 $\pm$ 10.28
	Dmax(cGy)	2720.9 $\pm$ 1186.6	2672.2 $\pm$ 1205.5	2719.3 $\pm$ 1143.7	2638.3 $\pm$ 1185.7
Right Lung 1474.9 $\pm$ 557.0	Dmean(cGy)	338.0 $\pm$ 297.3	313.1 $\pm$ 279.5	344.5 $\pm$ 306.4	308.5 $\pm$ 279.4
	V10(%)	12.01 $\pm$ 13.04	10.94 $\pm$ 12.50	12.61 $\pm$ 13.47	11.21 $\pm$ 12.78
	Dmax(cGy)	1061.6 $\pm$ 612.3	970.4 $\pm$ 558.2	1080.9 $\pm$ 616.0	1020.8 $\pm$ 546.4
	Dmean(cGy)	155.2 $\pm$ 112.8	145.8 $\pm$ 108.5	156.5 $\pm$ 114.0	144.3 $\pm$ 106.5
Left Lung 1171.4 $\pm$ 495.1	V10(%)	1.75 $\pm$ 3.28	1.14 $\pm$ 2.47	1.81 $\pm$ 3.24	1.13 $\pm$ 2.22

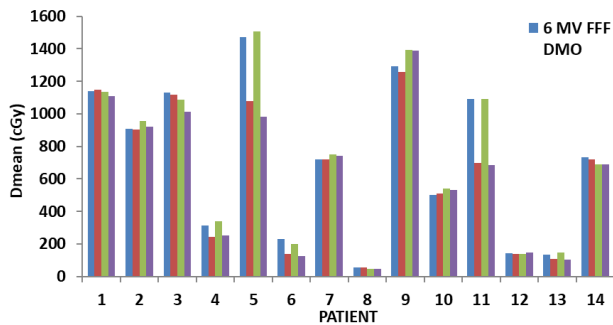


Figure 4. Mean dose of right kidney received with MCO and DMO (MCO: Multi-Criterial Optimization, DMO: Direct Machine Optimization, FFF: Flattening Filter Free).

When comparing SDMO with MCO plans utilizing 10 MV FFF energy, only MU and a few OAR parameters shows statistically significant difference. A p-value of 0.002 was observed upon analyzing the MU for both plans, with a mean and standard deviation value of 2365.41 ± 651.97 for MCO plans, which is higher than the average of plans generated using normal optimization, which is 2119.88 ± 487.69 . In this case, however, target outcome metrics like target coverage, CI, or HI did not show any relevance. A few OAR measures, such as the Dmax in cGy received by bowel loops and the Dmean in cGy received by the esophagus, right kidney, left kidney, left lung, and percentage volume receiving 10 Gy (V10) of the right kidney, have decreased.

Additionally, comparisons between groups were made. Plans using 6 MV FFF and 10 MV FFF photon beams were contrasted with one another for MCO and standard iterative optimization. None of the target outcome measures showed any statistical significance in either of the two methods as shown in table 4. Only a few of the OAR constraints demonstrated significance. Dmax in cGy received by the stomach, Dmean in cGy received by the right kidney, and V10 for the right lung, all increased on comparing normal plans employing 6 MV FFF and 10 MV FFF photon energies. The latter case shows a considerable reduction in Dmean in cGy received by the right kidney, Dmax in cGy received by the skin when comparing MCO plans using 6 MV FFF and 10 MV FFF photon energies.

Based on the statistical findings of doses to the OARs, there is no statistically significant difference found for many parameters among the four plans for each patient. These results imply that, although there might be small differences in the dose that organs receive when utilizing MCO, these findings might not be significant when determining the general level of OAR sparing.

Table 4. p-values significance of Organ at Risk with MCO for 6 and 10 MV FFF.

OARs	Parameter	p-value			
		6 DMO/ MCO	10 DMO/ MCO	6/10 DMO	6/10 MCO
Liver-GTV	D50	0.194	0.069	0.382	0.237
	Dmax	0.035	0.108	0.039	0.394
Stomach	Dmean	0.426	1.000	0.492	0.825
	Dmax	0.078	0.263	0.340	0.296
Duodenum	Dmean	0.683	0.081	0.078	0.314
	Dmax	0.326	0.944	0.104	0.660
Esophagus	Dmean	0.268	0.017	0.101	0.805
	Dmax	0.153	0.208	0.060	< 0.001
Spinal Cord	Dmax	0.268	0.081	0.867	0.952
Bowel Loops	Dmax	0.030	0.030	0.502	0.326
	Dmax	0.119	0.780	0.205	0.463
Heart	Dmean	0.008	0.078	0.411	0.104
	V10	0.014	1.000	0.944	0.353
	V20	0.281	0.584	0.178	0.584
	Dmax	0.296	0.081	0.584	0.512
Right Kidney	Dmean	0.025	0.005	< 0.001	< 0.001
	V10	0.025	0.011	0.170	0.918
Left Kidney	Dmax	0.049	0.093	0.520	0.109
	Dmean	0.042	0.030	0.808	0.715
	V10	0.106	0.059	0.402	0.590
Right Lung	Dmax	0.035	0.208	0.715	0.128
	Dmean	0.426	0.108	0.132	0.453
	V10	0.108	0.130	0.003	0.320
Left Lung	Dmax	0.030	0.124	0.569	0.101
	Dmean	0.042	0.050	0.493	0.638
	V10	0.161	0.151	0.636	0.673

DMO: Direct Machine Optimization, MCO: Multi Criterial Optimization, FFF: Flattening Filter Free.

DISCUSSION

This study explored the effectiveness of Multi-Criteria Optimization (MCO) in VMAT-based SBRT planning for liver cancer, comparing it with standard iterative optimization using Monte Carlo (MC) dose calculation in constrained mode. The findings are consistent with previous research across multiple disease sites, including prostate and lung cancers, and reinforce the potential of MCO to enhance treatment planning by improving organ-at-risk (OAR) sparing while maintaining comparable target coverage.

Park *et al.* demonstrated that MCO-based VMAT planning for prostate cancer can reduce dose to surrounding healthy tissues without compromising planning target volume (PTV) coverage, though they emphasized the need for clinical trials to assess toxicity and long-term outcomes ⁽³⁴⁾. Similarly, Marrazza *et al.* developed a template-based MCO VMAT SBRT approach for lung lesions. Their comparison of template-generated and manual plans showed improved dose conformity and gradient index, along with significantly reduced OAR doses. The study also noted that high fluence smoothing

settings yielded plans comparable to manual plans, while medium smoothing increased modulation complexity and treatment time⁽³⁵⁾.

Building on these insights, the current study evaluated MCO-based SBRT plans for hepatocellular carcinoma using both 6 MV FFF and 10 MV FFF photon energies. All plans-maintained OAR doses within recommended constraints, suggesting that MCO can achieve clinically acceptable plans while exploring trade-offs in real time. Across all patients, 6 MV FFF MCO plans produced slightly more conformal dose distributions with better OAR sparing, particularly for kidneys, and showed steeper dose fall-off around the PTV. This marginal advantage in plan quality may be attributed to the convex geometry of SBRT targets in liver cancer, which facilitates more efficient convergence of the MCO algorithm toward optimal solutions.

Nonetheless, our analysis found only minor differences in PTV coverage and dose homogeneity between MCO and standard plans. This aligns with the findings of Ghandour *et al.*, who observed that MCO does not significantly improve target coverage due to its reliance on fluence-based optimization, which may not fully account for tissue heterogeneity in Monte Carlo calculations^(36, 37). While MCO plans offered slightly better OAR sparing, they also resulted in increased monitor units (MUs), indicating longer treatment times—an undesirable trade-off in clinical workflows. Ghandour *et al.* also suggested that this increase in MUs may stem from MCO's preference for control points with more open leaf pairs, which leads to higher modulation complexity⁽³⁶⁾.

Moreover, Graphics Processing Unit -accelerated MCO planning algorithms, as assessed by Spalding *et al.*, demonstrated significant reductions in overall planning time up to 75% without compromising dosimetric quality⁽³⁸⁾. This suggests that MCO could be particularly valuable in busy clinical environments where time efficiency is crucial. In our study, although standard iterative optimization and MCO plans for both photon energies showed similar PTV outcomes, 10 MV FFF MCO plans offered slightly better OAR sparing without a noticeable rise in MUs compared to their 6 MV counterparts.

However, the tumor location, anatomy, and beam arrangement (single vs. dual arc) can influence planning outcomes, and these factors must be carefully considered in broader applications. Additionally, our limited patient cohort is a key limitation; thus, larger studies are required to confirm these findings and assess their generalizability. The planning in our study used the constrained mode of the MC algorithm within the Monaco treatment planning system, as opposed to Pareto surface navigation, which may influence optimization outcomes.

Lastly, consistent with the blinded assessments conducted by Jeremiah Wala *et al.*, where oncologists

rated MCO-generated IMRT prostate plans superior across multiple metrics⁽³⁹⁾, our findings reinforce the clinical value of MCO. Despite a slight increase in MUs, MCO-based VMAT SBRT plans, particularly those using 6 MV FFF energy, appear to offer a more favorable balance of plan quality and efficiency for liver tumors. With reduced planning time and improved OAR sparing, MCO presents a promising option for automated, high-quality SBRT treatment planning.

CONCLUSION

The study comparing SDMO and MCO techniques with 6 MV and 10 MV FFF photon energies demonstrated that MCO enhanced the conformity index and escalated the number of monitor units, implying longer beam delivery durations. While MCO plans exhibited improved sparing of specific organs-at-risk, such as reduced doses to the bowel loops, stomach, kidneys, and lungs, the overall impact on target coverage and dose distribution was not significantly different. Statistical significance was primarily observed for MU and a few OAR parameters, but there was no substantial disparity in target-related metrics like V95% or Dmax. In summary, although MCO provided certain advantages in OAR sparing, these differences were not statistically significant across most parameters, suggesting that the general degree of OAR sparing may not be meaningfully enhanced by employing MCO.

Acknowledgements: We thank all the MD, Medical physicist, Staff Nurses and CT technician in the Department of Radiation Oncology, Kasturba Medical college Manipal for supporting the study

Funding: None.

Ethical consideration: This article does not contain any studies with human participants or animals performed by any of the authors. The whole study was carried out with the approval of Institutional Research Committee, Manipal Academy of Higher Education [Ref: MCHP-Mpl/IRC/PG/2023/222] and Approved by Institutional Ethics Committee - 2 (Student Research), Kasturba Medical College and Kasturba Hospital [IEC2: 227/2024].

Conflict of interest: The authors declare no conflict of interest.

Authors contribution: N.N.: Literature review, data collection, statistical analysis, software, data interpretation, data interpretation, writing-original draft; S.S.N.: Conceptualization, Design, formal analysis, supervision, review and editing; Sh.: Drafting, writing- review and editing, supervision; J.N.: Formal analysis, data interpretation, review; S.S.N.: Supervision, drafting; S.H.: Formal analysis; S.L.: analysis, review and editing; A.S.: Review and editing. All authors have read and agreed to the

published version of the manuscript.

Data availability: Due to the nature of this research, we do not wish data to be shared publicly; thus, supporting data is not available.

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