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Comparison of VMAT and IMRT plans for SBRT treatment of multiple liver metastases using a single isocenter

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► ***Original article***

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ABSTRACT

***Background*:** To perform a comparison of the plan quality between volumetric modulated arc therapy (VMAT) and intensity modulated radiotherapy (IMRT) for multiple liver metastases using single-isocenter stereotactic body radiotherapy (SBRT). ***Materials and Methods*:** Twenty-one patients who developed two or three adjacent liver metastases were included. For every patient, both VMAT and IMRT plans were replanned respectively for SBRT treatment. Dosimetric parameters, including the mean dose for the planning target volume, conformity index (CI), homogeneity index (HI) and gradient index (GI), were evaluated. Normal tissue sparing was also investigated. Finally, the total delivered monitor units (MUs) for both groups of treatment plans during irradiation were measured and compared. ***Results*:** Both groups of treatment plans satisfied normal tissue tolerance and produced clinically accepted dose distributions. The VMAT plans provided higher values of HI and GI as well as similar CI values in comparison with the IMRT plans. In addition, the VMAT plans obtained ultimately a improved mean dose to the target and a reduced dose to the organs at risk. However, there were no statistically significant differences in the V_{7Gy} and D_{700cc} of healthy liver, the mean dose and V_{15Gy} of the ipsilateral kidney, the mean dose to the stomach, and the maximum dose to the heart between the two groups. Finally, the VMAT plans showed fewer MUs than the IMRT plans. ***Conclusions*:** The plan quality of single-isocenter VMAT plans is superior to that of IMRT plans for the SBRT treatment of multiple metastatic liver tumors from the perspective of pure physical parameters.

INTRODUCTION

Liver metastasis is a life-threatening disease associated with up to 30-70% of cancer deaths according to autopsy studies [1]. Multiple liver metastases appear commonly with tumor spread by hematogenous dissemination. It has been reported that patients, who had solitary or oligometastatic liver disease (up to 5 metastases), could obtain a benefit from long-term disease control and survival if aggressive treatments are managed [2]. Surgical resection has been recommended as the standard treatment for liver metastases for the purpose of curing, which is shows a 5-year overall survival rate of nearly 30-40% [3-5]. Unfortunately, only a minority of patients suffering from liver metastasis are considered to have resectable tumors. In this situation, stereotactic body radiotherapy (SBRT) is regarded as a feasible alternative method for treating for liver metastases of small volumes. SBRT, also named stereotactic ablative radiotherapy, focuses ablative radiation on the target volume site while minimizing the radiation dose to the surrounding organs due to the sharp dose gradient and high conformity. SBRT is noninvasive and has been proven to attain similar clinical outcomes to surgical resection [6]. With the advent of compensation of respiratory movement as well as target imaging and real-time tracking techniques, liver metastasis SBRT has been known as an effective and safe treatment method with improved reproducible treatment position that is able to reduce treatment-related toxicities.

Over the last decades, various machines have been developed for SBRT, such as CyberKnife, helical tomotherapy, and linear accelerator (LINAC). For LINAC, the common techniques for SBRT plans include three-dimensional conformal radiation therapy (3D CRT), intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy (VMAT). IMRT and VMAT are classified into inverse intensity treatment techniques, with each beam field segmented into several subfields of a few millimeters. They are considered an improvement over conventional 3D CRT because they are more conformal to tumor shape. The delivery methods of IMRT consist of step-and-shoot (static) and sliding window (dynamic) approaches. Both approaches execute delivery at a given fixed gantry angle and then move to the next angle sequentially. However, there are also differences between these two approaches. The step-and-shoot approach keeps the multileaf

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collimator (MLC) position stationary when the beam is on, while the sliding window approach allows the MLC position to move during irradiation. In contrast, VMAT delivers varying gantry angles, MLC positions and maximal dose rates simultaneously.

Recently, the treatment technique of multiple metastases based on a single isocenter has attracted increasing attention for tumors in different sites of the brain, lung, breast, spinal cord, and so on [7-13]. Such a treatment planning strategy has been proven to offer superior convenience and reduce motion error for patients because of its faster delivery. However, no published research has focused on liver tumors until now. The adoption of image-guided radiation therapy, which allows improved precision in the course of SBRT for liver tumors, makes the single-isocenter and multiple-target SBRT treatment for liver metastases possible. In this study, we comprehensively evaluated both the features of dose distributions and delivery efficiency between VMAT and IMRT planning groups. This study aimed to determine an appropriate technique to offer effective treatment of multiple liver metastases.

MATERIALS AND METHODS

Simulation and imaging acquisition

A total of 21 patients with two or three liver metastases (≤4 cm diameter) from various primary cancers who were treated previously in the radiation oncology department in Shanghai East Hospital from October 2016 to April 2019 were enrolled in this simulation study.

The summarized descriptive data of all patients are described in table 1. The average volume of each lesion was 14.702 ± 2.128 cc (range from 10.416 to 18.988 cc) for all patients, and the average total volume of the planning target volume (PTV) (including 2 -3 lesions) for each patient was 32.393 ± 4.237 cc (range from 23.554 to 41.232 cc).

All patients were simulated prone with arms above their heads using individualized vacuum molds (BlueBAG, Elekta, Stockholm, Sweden), and four-dimensional computed tomography (4D-CT) (Varian Medical Systems, Palo Alto, USA) images were collected on a GE Discovery CT750HD CT system (GE Healthcare, Waukesha, WI, USA) at a slice thickness of 1.25 mm.

Target and organs at risk delineation

Based on the images of the 4D-CT datasets, the target volumes (in the minimum intensity projection CT image) and organs at risk (OARs) structures (in the average intensity projection CT image) were contoured. Meanwhile, datasets from other modalities, incorporating magnetic resonance imaging and/or positron emission tomography datasets, were also fused to help identify structures using the Eclipse treatment planning system version 13.5 (Varian Medical Systems, Palo Alto, CA, USA). The gross target volume (GTV) includes the whole tumor displayed on the composite image. No additional margin needs to be expanded to determine the clinical target volume (CTV). The PTV was generated on the basis of the CTV with 3mm expansion margins in all directions. OARs, including the healthy liver (full liver minus GTV), spinal cord, stomach, ipsilateral kidney, heart and bowel, were outlined.

Table 1. Patient characteristics of 21 patients.

Patient	Number
Gender	
Male	14 (66.7%)
Female	7 (33.3%)
Age (year)	
Mean	62.571 ± 2.78
Range	56.77-68.37
Target	
Total number	46
Mean volume of each lesion (cc)	14.702 ± 2.128
Range	10.416-18.988
Mean total volume of each lesion (cc)	32.393 ± 4.237
Range	23.554-41.232
Tumor location	
Left lobe	2
Left medial lobe	1
Right anterior lobe	2
Right posterior lobe	5
Other (joint region)	11
Primary Tumor	
Colorectal	8
Hepatocellular	3
Ovarian	2
Lung	2
Other	6

Planning criteria

All CT image datasets were replanned using two types of single-isocenter techniques incorporating IMRT and VMAT and accomplished by experienced medical physicists. The IMRT plans were designed with the sliding-window technique. Only one isocenter was created and set up near the computed geometric center of the total metastases for every patient. The two groups of plans were designed by experienced medical physicist on the Eclipse system. IMRT plans were designed with 8-10 coplanar beams while VMAT plans created with two to three coplanar partial arcs. All these plans were delivered usingsix MV flattening filter-free (FFF) photon beams, accompanied with a high dose rate of 1400 MU/min. Dose distributions were optimized employing a photon optimizer and calculated with the analytical anisotropic algorithm with a slice spacing of 1.25 mm and 120-leaf high-definition MLC. The 100% prescription dose should cover 95% of the PTV in all the plans, while the dose constraints for OARs were followed according to table 2. The same dose regime of 60 Gy in 3 fractions was given for all plans, which has been proven to achieve a high local control rate of 93% [14].

The applied dose constraint protocols are listed in

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table 2 and were recommended by the Radiation Therapy Oncology Group 0236, the Quantitative Analyses of Normal Tissue Effects in the Clinic [15] and Rusthoven's clinical trial [16].

Table 2. The dose constraints protocol for organs at risk used for planning.

Organs at risk	Dose constraints
Healthy liver	D_{700cc}≤15Gy
Stomach	D_{mean}<15Gy
Bowel	D_{max}<30Gy (D_{5cc}<22.5Gy)
Ipsilateral kidney	$D_{35\%}$<15Gy
Spinal cord	D_{max}≤18Gy
Heart	D_{Max}≤30Gy

Abbreviations: Dx Dose to volume of x, Dmean Mean dose, Dmax Maximum dose.

Dosimetric evaluation

The dose distribution of each plan was assessed depending on several dosimetric parameters, which were calculated based on the target and OARs data according to the dose-volume histogram of every patient on the framework we developed.

The conformity index (CI) described the relation between the volume enclosed by the prescription isodose and the PTV using equation 1[17].

$$CI=\frac{\left(V_{PTV}^{Rx}\right)^2}{V_{PTV}\times V^{Rx}} \quad (1)$$

Where V^{Rx} represents the volume of the prescription isodose and V_{PTV} is the PTV. $V^{Rx}{}_{PTV}$ describes the overlapped volume between PTV and the prescription isodose volume.

The homogeneity index (HI) is calculated to evaluate the uniformity of the dose distribution in the target region according to equation 2[18].

$$HI=\frac{D_2\text{-}D_{98}}{D_{Rx}} \quad (2)$$

where D_2 and D_{98} mean the doses to the 2% and 98% PTVs, respectively, and D_{Rx} is the prescription dose.

The gradient index (GI) is proposed to analyze the dose drop off (equation 3)[19].

$$GI=\frac{V_{50}}{V_{100}} \quad (3)$$

Where V_{50} refers to 50% of the volume covered by the 50% prescription isodose line. V_{50} is the volume covered by the 100% prescription isodose line.

The healthy liver volume percentages of 21 Gy, 15 Gy, and 7 Gy isodose lines (V_{21Gy}, $V15_{Gy}$ and V_{7Gy}), the dose to 700cc (D_{700cc}) and the mean dose (D_{mean}) were calculated. The spinal cord, bowel, stomach, ipsilateral kidney and heart were also evaluated by means of mean doses (D_{max}), maximum doses (D_{mean}) or volumes covered by a 15 Gy isodose line (D_{15Gy}), respectively. The MU numbers for all plans were recorded to evaluate delivery efficiency.

Statistical analysis

All parameters were extracted and calculated based on DVH. Data analysis was carried out using SPSS software, version 26 (IBM Corp, Armonk, NY, USA). We applied a paired t test in order to test the differences between various parameters and chose a P value <0.05 as the threshold to imply statistical significance.

RESULTS

All the dosimetric parameters and OAR sparing data were calculated using the formulas above, which are summarized in table 3. Comparison of the two techniques revealed that the mean CI values did not differ significantly between the VMAT and IMRT plans, with values of 0.826 ± 0.013 and 0.832 ± 0.014 (p = 0.262), respectively, indicating equivalent conformity. The VMAT plans appeared a more nonuniform dose distribution within the target (HI = 0.341 ± 0.177) than the IMRT plans (HI = 0.216 ± 0.144) (p = 0). The VMAT plans yielded a significantly higher GI (GI = 4.723 ± 0.207) than the IMRT plans (GI = 6.122 ± 0.411) (p = 0).

The VMAT plans delivered a significantly increased dose to the PTV on average in comparison to the IMRT plans (6803.61 ± 54.264 cGy vs. 6524.929 ± 32.653 cGy, p = 0), while the mean maximum dose in the VMAT plans was observed to be significantly larger against the IMRT plans (8576.543 ± 114.772 cGy vs. 7418.681 ± 104.642, p=0).

Both groups of plans met the criteria of dose constraints for the OARs (table. 2). The resulting values confirmed that the received doses of the healthy liver in the VMAT plans were lower than those in the IMRT plans (V_{15Gy}, V_{21Gy} and mean dose), as shown in table 3. The values of V_{7Gy} and D_{700cc} exhibited equal doses with no difference (p=0.127 and 0.939) for the two groups. For the other OARs, the VMAT plans also delivered significantly lower maximum doses to the spinal cord and bowel as well as a lower mean dose to the heart. Nevertheless, the plans of both modalities indicated no statistical significance in regard to the mean dose to the stomach, the maximum dose to the heart and the mean dose and V_{15Gy} to the ipsilateral kidney.

The VMAT plans also delivered significantly faster, with an average 5479.067 ± 320.931 MU in comparison to the 6607.2 ± 4.6411 MU of the IMRT plans (p = 0.019).

A patient with two lesions of PTV1 and PTV2 was selected to exhibit the comparison of the dose distributions of the VMAT and IMRT plans (figure 1). Figure 1 reveals that the VMAT plans have more limited regions of 21 Gy and 15 Gy isodose lines but equal isodose lines of 7 Gy compared to the IMRT plans.

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Table 3. Comparison of dosimetric parameters and OAR sparing between VMAT and IMRT plans.

	VMAT	IMRT	*p*
CI	0.826±0.013	0.832±0.014	0.262
HI	0.341±0.177	0.216±0.144	0
GI	4.723±0.207	6.122±0.411	0
PTV			
D_{mean} (cGy)	6803.61±54.264	6524.929±32.653	0
D_{max} (cGy)	8576.543±114.772	7418.681±104.642	0
Liver			
D_{mean} (cGy)	969.633±69.862	1044.591±62.578	0.002
V_{21Gy} (%)	15.477±1.480	17.295±1.359	0.000
V_{15Gy} (%)	22.453±1.967	25.059±1.834	0.000
V_{7Gy} (%)	38.141±13.285	40.046±2.632	0.127
D_{700cc} (cGy)	231.622±49.642	229.967±52.726	0.939
Spinal cord			
D_{max} (cGy)	725.971±52.738	939.552±84.798	0.004
Ipsilateral kidney			
D_{max} (cGy)	175.891±44.420	218.576±50.541	0.084
V_{15Gy} (%)	1.674±0.695	2.054±0.809	0.074
Bowel			
D_{max} (cGy)	2154.5±371.698	2534.648±409.754	0.004
Stomach			
D_{mean} (cGy)	253.305±49.766	250.852±38.334	0.896
Heart			
D_{max} (cGy)	901.491±334.641	880.767±327.635	0.501
D_{mean} (cGy)	115.814±30.718	135.562±36.991	0.014
MUs	5479.067±320.931	6607.2±324.6411	0.019

Abbreviations: VMAT volumetric modulated arc therapy, IMRT intensity modulated radiotherapy, CI conformity index, HI homogeneity index, GI gradient index, PTV planning target volume, Dmean mean dose, Dmax maximum dose, Vx volume receiving dose of x, D700cc dose to volume of 700 cc, MU monitor units.

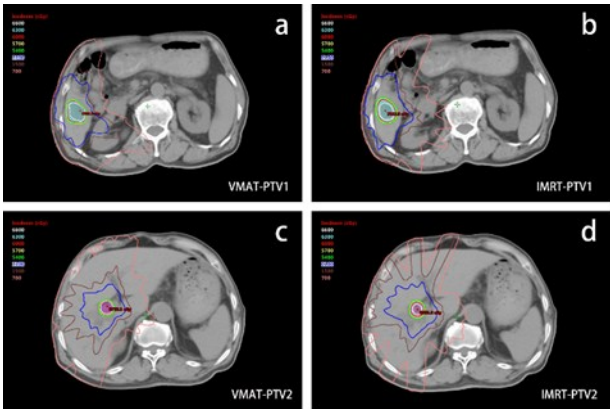

Figure 1. Dose distributions of axial computed tomography scans for VMAT and IMRT plans for one case. **(a)** Isodose lines of the VMAT plan for PTV1, **(b)** isodose lines of the IMRT plan for PTV1, **(c)** isodose lines of the VMAT plan for PTV2, **(d)** isodose lines of the IMRT plan for PTV2. Isodose lines show 110% (66 Gy, white), 105% (63 Gy, cyan), 100% (60 Gy, red), 95% (57 Gy, yellow) and 90% (54 Gy, green) of the prescription dose and 21 Gy (blue), 15 Gy (brown) and 7 Gy (pink) isodose lines.

DISCUSSION

VMAT and IMRT plans have been compared in many previous studies. Most results have suggested that WMAT plans exhibit equivalent or even better plan quality than IMRT plans combined with higher delivery efficiency [20, 21]. However, all of those studies were based on cases with a single lesion.

Certain tumor types often occur as more than one tumor. For such cases of multiple lesions, treatment plans can be complicated. The traditional treatment plan method is mainly the multiple isocenter plan, which can ensure an accurate irradiation position. However, there is a problem of incidental dose overlap between nearby treatment fields, which can increase the exposure of healthy tissue. The use of single-isocenter plans can avoid this problem. In addition, the irradiation time of a multiple-isocenter plan increases significantly with the number of lesions, while the irradiation time of a single-isocenter plan is much shorter [22]. Finally, a single-isocenter treatment plan can reduce treatment costs, which is also an important practical benefit [22]. Therefore, it is valuable to study whether single-isocenter or multiple-isocenter treatment should be used in treatment planning.

Multiple liver metastases are common in many advanced-stage tumors and often need to be treated by SBRT. When the multiple-isocenter plan is applied, the dose to normal liver tissue is often over the dose limit, so the dosimetric study of a single-isocenter treatment plan that can improve the damage to the liver is needed. The targets of multiple liver metastases can be seen as highly complex-shaped targets with very different dose distribution features from those of single lesions. To choose a suitable planning technique, we investigated the plan quality between VMAT and IMRT for single-isocenter multiple liver metastases SBRT in our study.

It is well known that comparative dosimetric studies are complex and are easily affected by various factors, resulting in biased results. To avoid this situation as much as possible, we standardized the conditions as much as possible in both plans in our study, referring to the latest planning study guidelines proposed by Hansen *et al.* for standardizing research processes and standards [23].

According to the analysis of the data above, both treatment techniques produced clinically acceptable plans, but the VMAT plans exhibited superior dose distribution to the IMRT plans.

For the PTV, the VMAT plans were observed to be higher, which means improved biological effects of the tumor target. This is consistent with the results of Bota's study for cases of a single lesion [24].

Both groups of single-isocenter plans produced highly conformal dose distributions. Xie *et al.* reported a mean CI value of 0.831 ± 0.093 when the jaw positions were selected automatically, which is similar to the mean CI value of 0.826 ± 0.013 in our study [25]. Raza *et al.* compared the single-isocenter dynamic conformal arc therapy plans with the VMAT plans for multiple brain metastases and obtained CI values ranging from 0.50 to 0.85 [12]. The IMRT plans also obtained an unexpected mean CI value of 0.832 ± 0.014 with no statistically significant difference from that of the VMAT plans. However, this is distinct from the comparative results of these single-target plans

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observed in other studies [26, 27], which resulted in better CI values for the VMAT plans. The possible reasons for the different results are the factors of the width of the MLC, the simple or complicated shape of the PTV and the number of treatment fields for IMRT plans, which influenced the target conformity.

The VMAT plans appeared to have a steeper dose gradient with a mean GI value of 4.723 ± 0.207, which is lower than that of the IMRT plans, accompanied by higher mean HI values. First, it is believed that the GI value may be correlated with the HI value for high-dose stereotactic radiotherapy [28]. In addition, the SBRT technique permits the presentence of dose nonuniformity based on its own dosimetric features if the hot spot is located in the target center. Therefore, a higher HI is not considered to be an adverse factor for plan quality.

Healthy liver is the principal OAR that needs prevention from the serious toxic effects of radiation hepatitis or radiation-induced liver disease. It can be affected by radiation as it is located near and surrounding the therapeutic target. The compared results indicated that the VMAT plans generally protected the healthy liver more than the IMRT plans in regard to V_{21Gy}, V_{15Gy} and mean dose. The VMAT technique also reduced the radiation to the spinal cord (D_{max}), heart (D_{mean}) and bowel (D_{max}) with the same target coverage compared to the IMRT technique. Besides, the two techniques resulted in similar doses to other OARs: stomach (mean dose), heart (maximum dose), and healthy liver (V_{7Gy} and D_{700cc}). Based on the observations above, we concluded that VMAT is superior in high- or medium-dose regions encompassing these OARs relatively closer to the PTV (healthy liver, spinal cord and bowel) but has equal effect in the low-dose regions encompassing OARs farther from the PTV (stomach, ipsilateral kidney, and 7 Gy isodose line of healthy liver) for single-isocenter, multiple-target SBRT pans. The same behavior can be seen in figure 1, which displays more limited isodose line regions of 21 Gy and 15 Gy for VMAT plans and approximate volumes covered by lower isodose lines of 7 Gy for WMAT and IMRT plans. Low-dose areas are known to be formed by MLC transmission. It appears to be indistinguishable from plans for a single lesion within the liver. Chen *et al.* conducted a dosimetric comparison of three treatment planning techniques incorporating 3-D conformal radiotherapy (3DCRT), IMRT and VMAT plans to determine which can acquire the lowest level of liver injury for the patients diagnosed with hepatocellular carcinoma. The results showed that the VMAT plans revealed safer to 3DCRT and VMAT plans regarding lower risk of related liver injury induced by radiation [29].

Additionally, the VMAT technique for multiple liver metastases offers another benefit over the IMRT technique in regards to treatment efficiency. It is known that the IMRT technique usually has a three times longer treatment time than the VMAT technique [30-32]. First, VMAT delivers a decreased number of MUs relative to IMRT, which agrees with our experimental results. In addition, the VMAT technique has improved delivery efficiency because the gantry angles, dose rate, and MLC positions can vary simultaneously during radiation. Higher treatment efficiency has been considered to be a significant advantage of the VMAT technique, especially for certain patients who cannot lie in bed for a long time because of pain or other reasons.

Although the single-isocenter treatment planning method, applied in the treatment for multiple liver metastases, is able to acquire excellent dose distribution, there still exist some uncertainties that limit its practical clinical application. The liver is situated in the upper abdominal cavity with relatively larger respiratory motion. The spatial location (distance or angle) between lesions will change constantly following respiration during radiotherapy delivery even though cone beam computed tomography verification has been performed, which eventually causes errors in real dose distributions [33]. It has been found that the 2.0° rotational error results in failure to achieve sufficient target coverage in 63% of cases, where D_{95}% (the dose to 95% of the target volume) and $V_{95\%}$ (the target volume covered by 95% of the prescribed dose) values cannot exceed 95% [34].

However, a few methods could be taken into consideration to minimize dosimetric errors. First, wider target margins can be used to compensate for inadequate target volume coverage [35]. Meanwhile, the hepatic function of liver metastasis patients is often better than that of patients with primary liver cancer, which means a higher radiation dose in the liver can potentially be used for liver metastasis with the same adverse effects. Moreover, the breath-hold technique is able to be performed to lower motion error in the course of beam delivery. It is achievable for a very shorter treatment time if FFF beams with dose rates as high as 2400 MU/min are used [36]. Therefore, single-isocenter SBRT treatment for multiple liver metastases still has feasibility and application prospects.

Simultaneously, some potential limitations of our study should be noted. Liver metastases have variability in tumor size, shape, position, and distance between lesions for every patient, which may influence our estimated results. This problem will be addressed in our future studies.

CONCLUSION

In this study, we systematically compared the single-isocenter VMAT and IMRT SBRT plans for multiple liver metastases in the aspect of both dose distributions and delivery efficiency. The VMAT technique was found to have higher plan quality in terms of increased dose to target, better normal

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tissue protection, better main dosimetric parameters and fewer MU numbers. Our study offers an approach to choose the proper planning method of treating multiple liver metastases.

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***Author contribution*:** Lian Zhu, Xin Lu and Zuo-Lin Xiang designed the study, performed the statistical analysis and drafted the manuscript. Aihua Wang helped to design the treatment plans. All authors read and approved the final manuscript.

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