

# A dose-volume intercomparison of volumetric-modulated arc therapy, 3D static conformal, and rotational conformal techniques for portal vein tumor thrombus in hepatocellular carcinoma

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(Received 14 October 2012; revised 16 December 2012; accepted 24 December 2012)

We created volumetric-modulated arc therapy (VMAT) plans for portal vein tumor thrombus (PVTT) in hepatocellular carcinoma, and compared the results with those from three-dimensional conformal radiotherapy (3D-CRT) and rotational conformal radiotherapy (R-CRT) plans. CT scan data from 10 consecutive patients with PVTT treated with 3D-CRT between January 2008 and January 2010 were utilized in the analysis. We analyzed the dosimetric properties of the plans for the 10 patients using the three different techniques with three different isocenter doses of 50, 56 and 60 Gy in 2-Gy fractions. The D<sub>95</sub>, D<sub>mean</sub>, homogeneity index and conformity index were compared for the planning target volume (PTV). The D<sub>mean</sub>, V<sub>20</sub> and V<sub>30</sub> were also compared for normal livers. The monitor units (MUs) and the treatment time were also evaluated. The normal liver V<sub>30</sub> for VMAT was significantly less than that for 3D-CRT for the prescribed doses of 56 and 60 Gy ( $P < 0.05$ ). It was also found that the normal liver V<sub>30</sub> resulting from 3D-CRT was prohibitively increased when the prescribed dose was increased in two steps. For PTV D<sub>95</sub>, we found no significant differences between the three techniques for the 50- and 56-Gy prescriptions, or between VMAT and the other techniques for the 60-Gy prescription. The differences in the MUs and treatment times were not statistically significant between VMAT and 3D-CRT. We have demonstrated that VMAT may be a more advantageous technique for dose escalation reaching 60 Gy in the treatment of PVTT due to the reduced normal liver V<sub>30</sub>.

**Keywords:** hepatocellular carcinoma; portal vein tumor thrombus; three-dimensional conformal radiotherapy; volumetric-modulated arc therapy

## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies in Asia [1]. Depending on neoplasm staging, the number or location of lesions, and remaining liver function, many different modalities have been employed for the treatment of HCC, such as surgical resection [2], transcatheter arterial chemoembolization [3], radiofrequency ablation [4], percutaneous ethanol injection [5], and a molecular-targeted anti-cancer drug (sorafenib) [6]. Once portal vein tumor thrombosis (PVTT) develops, treatment options are extremely limited. PVTT may result in the interruption or reduction of the portal vein blood flow,

which causes worsening of acute liver failure. PVTT may also increase the portal vein blood pressure, which leads to the aggravation of gastroesophageal varices. The survival time after a diagnosis of PVTT was reported to be shorter than 3 months without any treatment [7, 8]. The local control of PVTT facilitates the preservation of liver function and enables the implementation of various therapeutic options [9–12].

Recently, radiotherapy has been increasingly used for the treatment of PVTT because it enables a region of treatment to be easily specified. Furthermore, it was reported that partial liver irradiation of an intra-hepatic tumor with normal fractionation yielded significant dose-response

variations at doses between 30 and 70 Gy [13]. The use of three-dimensional static conformal radiotherapy (3D-CRT) for PVTT was also reported; the local control rate ranged from 37.5–57.9%, and the median survival period ranged from 6.7–10.7 months [14–20]. In addition, intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and tomotherapy were also employed for treating PVTT [21, 22]. However, to the best of our knowledge, dose-escalation studies using VMAT for PVTT have not been reported.

The purpose of this study was to investigate the impact of VMAT for PVTT on dose-escalation treatment-planning in terms of target dose parameters and toxicity to organs at risk (OARs), including the normal liver.

## MATERIALS AND METHODS

### Patient characteristics

CT data sets of 10 consecutive patients (8 males and 2 females) with PVTT treated with 3D-CRT between January 2008 and January 2010 were used. PVTTs associated with HCC were diagnosed by alpha-fetoprotein determination, evaluation of proteins induced by the absence of vitamin K, antagonist-2 examinations, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI). The age range of the patients was 59–75 years. Patient characteristics are shown in Table 1.

### Treatment planning

Planning CT images were acquired with a slice thickness of 3 mm under free breathing conditions without using a body fixation device. A linear accelerator, Synergy (Elekta, Stockholm, Sweden), was employed with a photon energy

of 10 MV for 3D-CRT and 6 MV for VMAT [23] and rotational conformal radiotherapy (R-CRT). Pinnacle 8.0 m (Philips, Eindhoven, The Netherlands) was utilized for 3D-CRT, whereas ERGO ++ 1.7.1 (Elekta) was used for VMAT and R-CRT. ERGO ++ employs anatomically based VMAT optimization, in which all the field shapes are pre-defined by a treatment planner based on the shapes of the target and OARs. Consequently, field shapes are neither complicated nor small. Therefore, leaf motion during gantry rotation is relatively slow compared with fluence-map-based VMAT leaf sequences. This slow motion of the multi-leaf collimator (MLC) leaves may be appropriate for a moving target, such as a PVTT.

A clinical target volume (CTV) containing the PVTT and its contiguous lesions was identified on the contrast-enhanced CT or MRI images. A planning target volume (PTV) was defined by adding a margin of 1 cm in the lateral and antero-posterior directions and 2 cm in the cranio-caudal direction to the CTV, based on our observation that, under fluoroscopy, respiration-induced cranio-caudal movements of the liver were within 2 cm for all the cases. OARs included the normal liver, kidneys, and duodenum. For ERGO ++ VMAT optimization, a ring-shaped region of interest (ROI) with a width of 1 cm was defined outside the PTV with a spacing of 1 cm.

All of the 3D-CRT plans employed a 4-field co-planar irradiation technique, and the gantry angles were manually selected based on the morphological relationship between the PTV and the OARs. For R-CRT, ERGO ++ calculated the dose distributions generated by rotational conformal beams with a constant MU per gantry angle. Three different doses of 50, 56 and 60 Gy were prescribed to the isocenter in 2-Gy fractions. There are few articles reporting appropriate normal tissue tolerances for patients with liver

**Table 1.** Clinical characteristics for the 10 patients with portal vein tumor thrombus (PVTT)

Gender	male	8
	female	2
Age		66.8 ± 5.3 (59–75)
Level of the PVTT	Vp2	2
	Vp3	6
	Vp4	2
Location of the PVTT	right branch	7
	left branch	3
	main branch	2 <sup>a</sup>
Volume of whole liver (cc)		1269 ± 206 (989–1719)
Volume of normal liver (cc)		1141 ± 197 (881–1598)
Volume of PTV (cc)		161 ± 45.2 (109–234)

<sup>a</sup>One patient had PVTT of the right and main branches, while another patient had PVTT involving the left and main branches.

**Table 2.** Dose constraints for organs at risk (OARs)

OARs	Dose constraints
Normal liver	V30 ≤ 30%
Duodenum	Dmax ≤ 63 Gy V40 ≤ 20%
Kidney	V20 ≤ 20%
Spinal cord	Dmax < 50 Gy

V30 = percent volume exceeding 30 Gy, Dmax = maximum dose, V40 = percent volume exceeding 40 Gy, V20 = percent volume exceeding 20 Gy.

dysfunction, and therefore, we employed dose constraints based on the QUANTEC normal tissue tolerances shown in Table 2 [24, 25].

### Plan evaluation

Plans created by ERGO++ were transferred to Pinnacle so that all three different plans were evaluated using the same dose calculation algorithm. The dose covering 95% of the volume (D95), mean dose (Dmean), homogeneity index (HI) and conformity index (CI) were calculated for the PTV. The CI was defined according to the Paddick formulation as follows [26]:

$$\text{Paddick CI} = (\text{TV}_{\text{PIV}})^2 / (\text{TV} \times \text{PIV}), \quad (1)$$

where  $\text{TV}_{\text{PIV}}$  is the target volume covered by a prescribed isodose volume, TV is the target volume, and PIV is the prescribed isodose volume. In this study, an isodose level of 95% was employed. Meanwhile, the HI was calculated as the Dmax/Dmin ratio, where Dmax and Dmin represent the maximum and minimum doses, respectively. For the normal liver, the Dmean, percent volume > 20 Gy (V20), and percent volume > 30 Gy (V30) were evaluated. For the duodenum, percent volume > 40 Gy (V40) and the maximum dose (Dmax) were evaluated. For the kidneys, V20 was evaluated. For the evaluation of treatment efficiency, the total monitor units (MUs) and treatment times were recorded and compared between the three delivery techniques.

### Statistical analyses

A Friedman test was performed to identify differences in the mean values between the three techniques for each of the three prescribed doses. When the Friedman test resulted in statistical significance ( $P < 0.05$ ), Dunn's multiple comparison test was applied for each pair of the three techniques with a threshold probability of 0.05. All statistical analyses were performed using GraphPad Prism version 5 (GraphPad Software, CA, USA).

## RESULTS

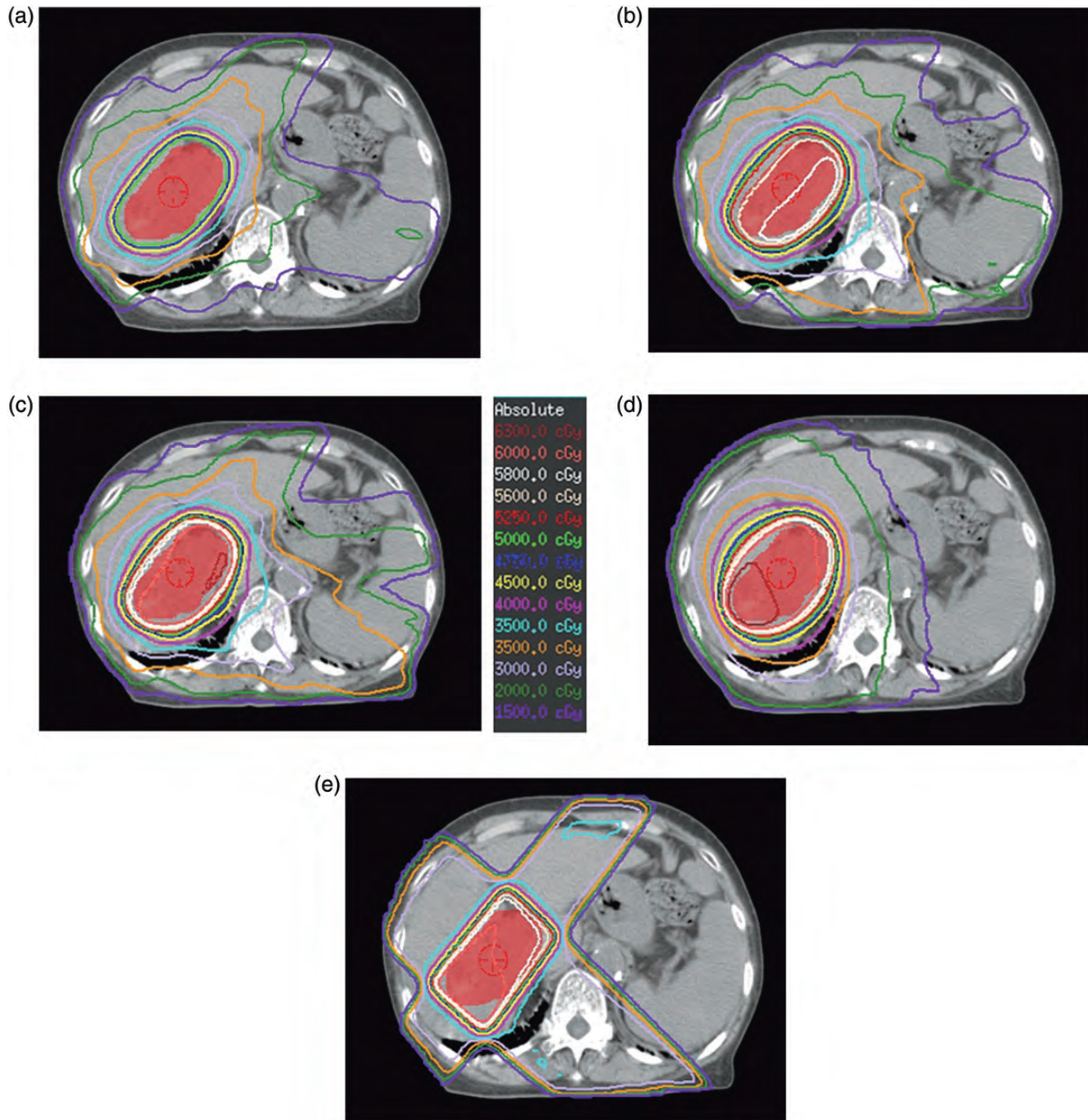
Fig. 1a to e present a comparison of the dose distributions for VMAT, R-CRT and 3D-CRT, where Fig. 1a to c show the results of VMAT for prescribed doses of 50, 56, and 60 Gy, respectively; (d) shows the results of R-CRT for a prescribed dose of 60 Gy; and (e) shows the results of 3D-CRT for a prescribed dose of 60 Gy. For each VMAT plan, the beam weights were optimized to satisfy the dose constraints shown in Table 2.

Fig. 2 shows a comparison of the dose volume histogram (DVH) for the PTV and the normal liver between 3D-CRT, VMAT and R-CRT for the prescribed doses of (a) 50 Gy, (b) 56 Gy and (c) 60 Gy. Each plot represents the average patient results. The normal liver V30 resulting from 3D-CRT was prohibitively increased when the prescribed dose was increased in two steps. Furthermore, the normal liver V30 associated with VMAT was significantly less than that associated with 3D-CRT for the prescribed doses of 56 and 60 Gy.

Table 3 shows the dose-volume parameters for the PTV, normal liver, kidney and duodenum in the 3D-CRT, VMAT, and R-CRT groups, each of which were prescribed three different doses of 50, 56 and 60 Gy. Each pair of bold data points indicates a statistically significant difference between the two groups based on Dunn's multiple comparison test ( $P < 0.05$ ). More complex statistical significances were not easily expressed in the table and are described under the table.

For the PTV D95, we found no significant differences between the three techniques for the 50- and 56-Gy prescriptions, and no significant differences were found between VMAT and the other two techniques for the 60-Gy prescription. The statistical significances for the CI varied depending on the prescribed dose; however, VMAT always yielded the highest CI score. The HI for 3D-CRT was always the best, and we found no statistically significant differences between 3D-CRT and VMAT.

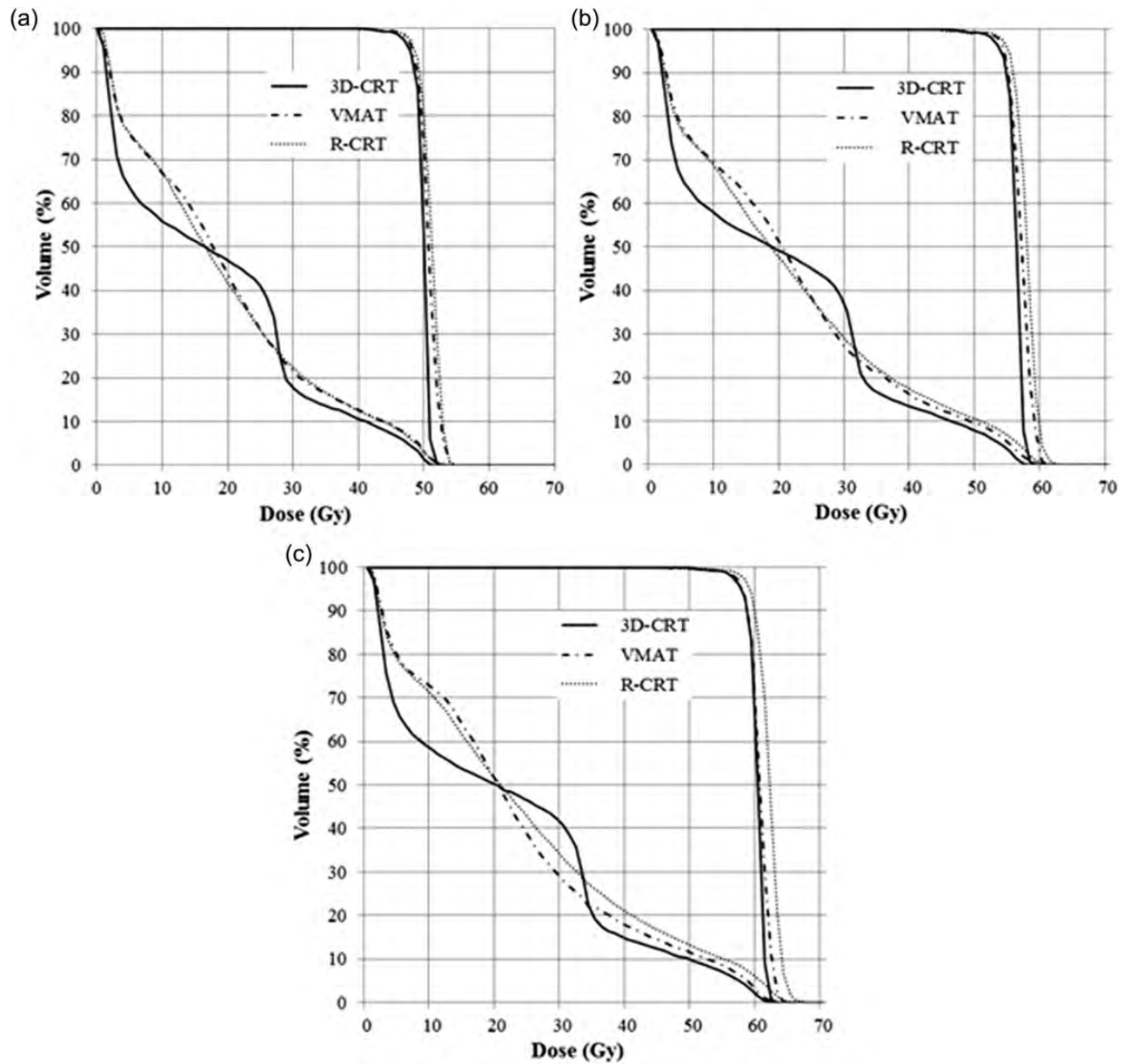
The normal liver V30 for VMAT was significantly less than that for 3D-CRT with prescribed doses of 56 and 60 Gy, and the difference in the V30 between VMAT and 3D-CRT rapidly increased during the 2-step dose escalation. Furthermore, the normal liver V20 was not significantly different between the three techniques for each dose prescription. We also found no significant difference in the normal liver Dmean between VMAT and 3D-CRT for any of the dose prescriptions. The right kidney V20 for VMAT was always less than that for 3D-CRT for all of the dose prescriptions ( $P < 0.05$ ). The left kidney V20 exhibited no significant differences between the three techniques. The duodenum V40 was also not significantly different between the three techniques, but VMAT did yield the lowest V40 ( $8.7 \pm 8.3\%$  at 50 Gy,  $11.0 \pm 9.6\%$  at 56 Gy,



**Fig. 1.** Comparison of dose distributions between VMAT, R-CRT and 3D-CRT. (a) VMAT with a prescribed dose of 50 Gy, (b) VMAT with a 56-Gy dose, (c) VMAT with a 60-Gy dose, (d) R-CRT with a 60-Gy dose, and (e) 3D-CRT with a 60-Gy dose. The filled red region shows the planning target volume. For each VMAT plan, beam weights were optimized to satisfy the dose constraints shown in Table 2.

and  $12.4 \pm 10.5\%$  at 60 Gy). The duodenum  $D_{max}$  was  $<54$  Gy for all the techniques with no significant differences. The differences in the MUs between the three techniques were not statistically significant ( $291.5 \pm 59.5$  for 3D-CRT,  $321.7 \pm 11.5$  for VMAT, and  $297.9 \pm 11.2$  for

R-CRT). The treatment times were  $123 \pm 7$  s for 3D-CRT,  $128 \pm 11$  s for VMAT, and  $97 \pm 26$  s for R-CRT; the difference in treatment time between VMAT and 3D-CRT was not statistically significant, but the difference between VMAT and R-CRT was significant ( $P < 0.05$ ).



**Fig. 2.** Comparison of the dose volume histogram (DVH) of the planning target volume (PTV) and normal liver between 3D-CRT, VMAT and R-CRT for three different prescribed doses of (a) 50 Gy, (b) 56 Gy, and (c) 60 Gy. Each plot shows the patient average. The normal liver V30 for 3D-CRT was prohibitively increased when the prescribed dose was increased in two steps. Conversely, the normal liver V30 for VMAT was significantly less than that for 3D-CRT for the prescribed doses of 56 and 60 Gy.

## DISCUSSION

Historically, radiotherapy for HCC was a whole liver treatment with poor outcome [27–29], and it was further reported that tolerated dose depended on the irradiated volume [30]. For the treatment of HCC, a dose–response relationship was reported [13, 31], and further study showed improved outcomes with dose escalation [32, 33]. Ren *et al* also mentioned that a dose increase up to 62 Gy might be clinically acceptable depending on the tumor volume [34].

Radiotherapy dose escalation for HCC and PVTT is limited by the maximum tolerable dose to the normal liver. Excess doses to the normal liver may result in radiation-induced liver disease (RILD) [35], and various dose measures have been proposed to avoid major liver complications, the most frequently used of which are the normal liver V30, Dmean, and NTCP [36].

Liang *et al.* proposed a normal liver V20 of 49%, normal liver V30 of 28%, and normal liver Dmean of 23 Gy as tolerance limits to avoid RILD when treating primary

**Table 3.** DVH parameters for the PTV, normal liver, kidney and duodenum for 3D conformal radiotherapy (3D-CRT), volumetric modulated arc radiotherapy (VMAT) and rotational conformal radiotherapy (R-CRT), each at the prescribed doses of 50, 56 and 60 Gy

		50 Gy			56 Gy			60 Gy		
		3D-CRT	VMAT	R-CRT	3D-CRT	VMAT	R-CRT	3D-CRT	VMAT	R-CRT
PTV	D95 (Gy)	47.9 ± 1.1	48.9 ± 1.0	49.1 ± 0.7	53.7 ± 1.2	54.6 ± 1.0	54.8 ± 0.7	<b>57.5 ± 1.3</b>	58.0 ± 1.2	<b>58.8 ± 0.7</b>
	Dmean (Gy)	<b>49.8 ± 0.5</b>	50.7 ± 1.0	<b>51.3 ± 0.4</b>	<b>55.6 ± 0.5</b>	56.1 ± 0.8	<b>55.8 ± 0.3</b>	<b>59.7 ± 0.5</b>	<b>60.2 ± 0.8</b>	<b>61.7 ± 0.4<sup>c</sup></b>
	CI	<b>0.63 ± 0.0</b>	<b>50.71 ± 0.0</b>	<b>70.68 ± 0.08<sup>a</sup></b>	0.63 ± 0.05	0.71 ± 0.08	0.68 ± 0.08	0.63 ± 0.05	<b>0.71 ± 0.07</b>	<b>0.68 ± 0.08</b>
	HI	<b>1.13 ± 0.04</b>	1.21 ± 0.11	<b>1.24 ± 0.10</b>	<b>1.13 ± 0.04</b>	1.21 ± 0.10	<b>1.24 ± 0.10</b>	<b>1.13 ± 0.04</b>	1.22 ± 0.10	<b>1.24 ± 0.10</b>
Liver	V20 (%)	46.9 ± 10.4	43.4 ± 5.8	43.3 ± 9.3	48.4 ± 11.0	49.4 ± 6.1	47.8 ± 9.2	49.8 ± 11.0	49.9 ± 6.6	50.5 ± 9.0
	V30 (%)	<b>17.6 ± 3.3</b>	<b>21.3 ± 4.1</b>	<b>24.5 ± 6.1<sup>b</sup></b>	<b>35.2 ± 8.4</b>	<b>26.2 ± 3.1</b>	29.7 ± 7.3	<b>40.9 ± 9.4</b>	<b>28.0 ± 4.2</b>	33.0 ± 7.9
	Dmean (Gy)	<b>17.9 ± 2.8</b>	19.3 ± 2.3	<b>19.8 ± 2.8</b>	20.1 ± 3.1	21.5 ± 2.3	22.1 ± 3.1	<b>21.5 ± 3.3</b>	22.7 ± 2.2	<b>23.7 ± 3.3</b>
R kidney	V20 (%)	<b>18.9 ± 17.3</b>	<b>8.6 ± 9.8</b>	10.8 ± 11.0	<b>17.6 ± 18.7</b>	<b>10.4 ± 11.0</b>	12.1 ± 11.6	<b>18.6 ± 19.3</b>	<b>10.4 ± 11.3</b>	12.7 ± 11.7
L kidney	V20 (%)	1.8 ± 2.8	1.2 ± 3.5	02.0 ± 3.1	1.1 ± 2.3	0	2.5 ± 3.4	3.1 ± 4.8	0.1 ± 0.2	
Duodenum	V40 (%)	12.0 ± 11.1	8.7 ± 8.3	9.6 ± 9.0	14.4 ± 12.5	11.0 ± 9.6	12.2 ± 10.4	16.5 ± 12.2	12.4 ± 10.5	13.4 ± 11.0
	Dmax (Gy)	44.0 ± 13.1	44.9 ± 13.7	44.4 ± 14.7	49.1 ± 14.6	50.2 ± 15.9	49.8 ± 16.5	52.9 ± 15.8	53.3 ± 16.7	53.3 ± 17.6

Each pair of bold data indicates a statistically significant difference between two of the three treatment modalities ( $P < 0.05$ ). Statistical significances between the three groups are described. <sup>a</sup>3D-CRT < VMAT, R-CRT < VMAT; <sup>b</sup>3D-CRT < VMAT, 3D-CRT < R-CRT; <sup>c</sup>3D-CRT < VMAT < R-CRT; D95 = Dose covering 95% of the volume, Dmean = mean dose, CI = conformity index, HI = homogeneity index, V20 = percent volume >20 Gy, V30 = percent volume >30 Gy, V40 = percent volume >40 Gy.

liver carcinomas with 3D-CRT [37]. The same research group also proposed a normal liver V20 of 48.5% for the same purpose based on different clinical data sets [38]. Our study showed that the normal liver V30 for 3D-CRT rapidly increased when the prescribed dose was escalated in two steps. However, the V30 for VMAT was not greatly increased and remained low compared with that for 3D-CRT during the dose escalation that reached 60 Gy. In our study, the normal liver V30 for the 60-Gy prescription was  $28.0 \pm 4.2\%$ , which was, on average, equal to a tolerance limit of 28%. Considering that Liang's study was based on hypofractionation with a fraction dose of 4–6 Gy, our protocol utilizing a fraction dose of 2 Gy may lead to better tolerated outcomes with a V30 of 28%. The normal liver V20 for a 60-Gy prescription with VMAT was  $49.9 \pm 6.6\%$ , which slightly exceeded the  $V20 < 49\%$  condition determined based on the hypofractionation condition. There was no significant difference in the normal liver Dmean between 3D-CRT and VMAT. The Dmean of  $22.7 \pm 2.2$  Gy for VMAT with a 60-Gy prescription is in accordance with Liang's recommendation of a Dmean  $< 23$  Gy.

Toxicity to the gastrointestinal tract frequently limits radiation doses to HCC [39–41]. The duodenum may receive a higher dose due to proximity to the PTV, particularly when the PTV involves the main branch or the right lobe. As most HCC patients have liver cirrhosis and portal hypertension, there would be a higher risk of gastroduodenal ulcers or portal hypertensive congestive gastropathy [42, 43]. This means that radiation toxicity of duodenum may become more severe for the HCC patients, but there are few articles reporting appropriate normal tissue tolerances for patients with liver dysfunction. Many studies of duodenum toxicity were aimed at stereotactic radiotherapy [44, 45]. With conventional fractionation, Chen *et al.* reported that the risk of severe late complications varied from 5–10% unless the dose exceeded 55 Gy [46]. For locally advanced pancreatic cancer, Florence proposed a dose prescription for the duodenum, where the percent volume exceeding 45 Gy was maintained less than 15% [47]. In the present study, the maximum dose to the duodenum for the 60 Gy prescription was  $53.3 \pm 16.7$  Gy for VMAT, which complies with Chen's findings. The duodenum V40 for 60 Gy prescription was  $12.4 \pm 10.5\%$ , that also complies with Florence's proposal. The above discussion suggests that VMAT can maintain the risk of duodenum toxicity at a relatively low level when the prescribed dose is escalated to 60 Gy.

A limitation of this study is that VMAT provides superior DVHs compared to 3D-CRT and R-CRT only in the range from 20–30 Gy (Fig. 2). It is well known that portal vein thrombosis may cause worsening of liver function according to the increase of portal pressure and impaired liver vascularization in a cirrhotic patient [48], which means that the liver function in HCC patients with PVTT

tends to deteriorate significantly compared to other patients without liver dysfunction. Many important researches have been published but we have not reached a consensus about radiotherapy for PVTT yet. Consequently, dose escalation to HCC with PVTT should be based on careful clinical evaluation [49].

## CONCLUSION

In conclusion, we have shown, for the first time, that 3D-CRT for PVTT needs to be avoided for dose escalation reaching 60 Gy due to the prohibitively increased normal liver V30. Although it is necessary to pay maximum attention to future reports about the relationship between liver dysfunction and radiation, VMAT for PVTT is a more advantageous technique for dose escalation due to the reduced and tolerable normal liver V30 compared with 3D-CRT. It is also anticipated that the anatomy-based VMAT employed in this study may be favorable for a tumor target that moves with respiration, such as PVTT.

## ACKNOWLEDGEMENTS

The authors are grateful to Kiyoshi Yoda of Elekta KK for his guidance and encouragement. They would also like to thank the staff of the Osaka City University Hospital, who provided assistance during this study.

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