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RapidArc® *vs* intensity-modulated radiation therapy for hepatocellular carcinoma: a comparative planning study

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Objective: The purpose of this study is to compare the dose-volumetric results of RapidArc® (RA Varian Medical Systems, Palo Alto, CA) with those of intensity-modulated radiation therapy (IMRT) for hepatocellular carcinoma.
Methods: 20 patients previously treated for hepatocellular carcinoma were the subjects of this planning study. 10 patients were treated for portal vein tumour thrombosis (Group A), and 10 patients for primary liver tumour (Group B). Prescription dose to the planning target volume was 54 Gy in 30 fractions, and the planning goal was to deliver more than 95% of prescribed dose to at least 95% of planning target volume.
Results: In Group A, mean doses to liver were increased with RA *vs* IMRT (22.9 Gy *vs* 22.2 Gy, $p=0.0275$). However, $V_{30\ Gy}$ of liver was lower in RA *vs* IMRT (31.1% *vs* 32.1%, $p=0.0283$). In Group B, in contrast, neither mean doses nor $V_{30\ Gy}$ of liver significantly differed between the two plans. $V_{35\ Gy}$ of duodenum and $V_{20\ Gy}$ of kidney were decreased with RA in Groups A and B, respectively ($p=0.0058$ and 0.0124, respectively). Both maximal doses to spinal cord and monitor unit were significantly lower in the RA plan, regardless of the group.
Conclusion: The dose-volumetric results of RA *vs* IMRT were different according to the different target location within the liver. In general, RA tended to be more effective in the sparing of non-liver organs at risk such as duodenum, kidney, and/or spinal cord. Moreover, RA was more efficient in the treatment delivery than IMRT in terms of total monitor unit used.

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With the advent of three-dimensional conformal radiotherapy and more understanding of partial liver tolerance, radiotherapy has been increasingly incorporated into the treatment of hepatocellular carcinoma (HCC). Reported results of novel techniques to deliver higher dose radiation, such as stereotactic body radiotherapy and proton beam therapy, are not only feasible but also promising [1, 2]. In contrast, HCC has rarely been an indication of intensity-modulated radiation therapy (IMRT) due to the organ motion during respiration, although several dosimetric studies have been reported on the benefit of IMRT in HCC [3, 4]. However, with image-guidance technology, liver tumours can be treated with IMRT safely and efficiently. Recently, a study on IMRT using Hi-Art tomotherapy (TomoTherapy Inc., Madison, WI) for patients with unresectable HCC reported lower toxicity with promising local control [5].

RapidArc® (RA; Varian Medical Systems, Palo Alto, CA), which delivers intensity-modulated beams during gantry rotation, is shown to reduce doses to organs at risk (OARs) compared with static field IMRT in a number of tumours at various anatomical sites [6–8]. However, little is known about the benefit of RA in the treatment of HCC to date. Herein, a planning study comparing RA *vs* IMRT for patients with HCC was performed.

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Methods and materials

Patient population

After institutional review board approval, 20 patients who underwent radiotherapy for HCC between December 2004 and February 2009 were entered into this planning study. There were 19 males and 1 female, and their median age was 59 (range, 38–74) years. Among them, 10 patients were treated for portal vein tumour thrombosis (Group A), and 10 patients were treated for primary liver tumour (Group B). Of 10 patients in Group B, 4 patients had left lobe tumours and 6 patients had right lobe tumours.

Simulation

All patients underwent three-phase CT, including free breathing, full inhalation and full exhalation. Clinical target volume included only portal vein tumour thrombosis in Group A, and only intrahepatic tumour in Group B. Internal target volume was delineated based on the three phases of CT images. Planning target volume (PTV)

Table 1. Dose–volume constraints

Volume	Dose–volume constraints	Relative weighting
PTV	$D_{100\%} \geq 102\%$ $D_{98\%} \geq 102.5\%$ $D_{2\%} \geq 103.5\%$ $D_{max} \geq 104\%$	120
CTV	$D_{100\%} \geq 102.5\%$ $D_{max} \geq 104\%$	130
Whole liver	$V_{30\ Gy} \geq 40\%$	80
Kidneys	$V_{20\ Gy} \geq 30\%$	60
Duodenum	$V_{35\ Gy} \geq 30\%$	50
Stomach	$V_{35\ Gy} \geq 30\%$	50
Spinal cord	$D_{max} \geq 45$ Gy	50

CTV, clinical target volume; PTV, planning target volume.

was defined as internal target volume plus 8 mm in all directions. Organs at risk were also delineated, including whole liver, non-target liver (whole liver minus PTV), stomach, duodenum, kidney, spinal cord, and so on.

Planning

Treatment planning was performed using the Eclipse system with 15 MV photons in a Varian 21IX machine with a 120 leaf millennium multileaf collimator (Varian Medical Systems, Palo Alto, CA). For IMRT, the sliding window technique was used. The Anisotropic Analytical Algorithm (AAA, version 8.6) dose calculation algorithm was used for both IMRT and RA. The dose calculation grid was set to 2.5 mm. A total of 54 Gy/30 fx was prescribed to the PTV with the planning goal of delivering more than 95% of the prescribed dose to at least 95% of the PTV. To achieve these objectives, a constraint for $D_{100\%}$, where $D_{n\%}$ is the dose received by the n% volume of the target volume, was set to receive ≥102% of prescription and a constraint for maximum dose (D_{max}) was set to receive ≥104% of the prescription in the optimisation process for both plans. Optimisation constraints and their weightings are summarised in Table 1. These constraints and weightings were set initially and then were modified by either relaxing or tightening or adding during the optimisation process based on the real-time updated dose–volume histograms (DVHs) of structures. We used a 2-cm-wide ring structure, pseudo target, which is 7 mm apart from the PTV.

For both IMRT and RA, the isocentre of beams was set at the centre of the PTV initially and then determined by rounding off to the nearest integer. For IMRT plans, five coplanar gantry angles of beams were manually selected based on morphological relationships of the PTVs and OARs. An RA plan was generated using 2.5 arcs rotating from 179.9° to 180.1° anticlockwise, from 180.1° to 179.9° clockwise, and 179.9° to 0° anticlockwise. All plans used 15 MV photons and a fixed dose rate (or maximum dose rate for RA) of 600 MU min^{-1}. Planning was done by a single physicist (JMP) and clinical aspects were reviewed by a single oncologist (KK).

Dose-volumetric analysis

Dose-volumetric analysis was performed using DVHs of the treatment plans of individual patients. Conformity index (CI) was calculated as (volume within the 95% isodose)/(volume of the PTV). For liver, both mean dose and $V_{30\ Gy}$ of the whole liver and non-target liver were calculated. For non-liver OARs, $V_{35\ Gy}$ of stomach and duodenum, $V_{20\ Gy}$ of kidney, and maximal dose to spinal cord were calculated. Average DVHs for each OAR were also built from the individual DVHs. A paired *t*-test was used to calculate the statistical difference of dose-volumetric results between RA and IMRT. Total monitor unit and treatment time were also compared to access the efficiency of treatment delivery.

Results

The dose-volumetric results of RA compared with IMRT in Groups A and B are shown in Tables 2 and 3, respectively. In group A, mean doses to the whole liver and non-target liver were increased with RA *vs* IMRT (22.9 *vs* 22.2 Gy and 18.7 *vs* 18.0 Gy, $p=0.0275$ and 0.0307, respectively). However, $V_{30\ Gy}$ of the whole liver and non-target liver was lower in RA *vs* IMRT (31.1% *vs* 32.1% and 21.4% *vs* 22.6%, $p=0.0283$ and 0.0351,

Table 2. Dose-volumetric comparison of intensity-modulated radiation therapy (IMRT) and RapidArc® [RA; (Varian Medical Systems, Palo Alto, CA)] in patients with portal vein tumour thrombosis (Group A)

Variable	Mean ± standard deviation		*p*–value
	IMRT	RA	
Conformity index	1.1±0.03	1.0±0.008	*<0.0001*
Mean whole liver dose (Gy)	22.2±6.6	22.9±6.0	*0.0275*
Mean non-target liver dose (Gy)	18.0±5.9	18.7±5.3	*0.0307*
Max spinal cord dose (Gy)	32.1±6.0	26.7±6.9	*0.0217*
$V_{30\ Gy}$ of whole liver (%)	32.1±12.1	31.1±12.2	*0.0283*
$V_{30\ Gy}$ of non-target liver (%)	22.6±10.2	21.4±10.1	*0.0351*
$V_{35\ Gy}$ of duodenum (%)	20.9±10.0	17.9±9.9	*0.0058*
$V_{35\ Gy}$ of stomach (%)	2.9±2.6	1.5±2.0	0.0891
$V_{20\ Gy}$ of kidney (%)	9.9±7.6	8.3±7.1	0.2388
Right kidney	18.6±13.9	16.5±13.8	0.3794
Left kidney	1.8±4.0	0.7±1.4	0.2785
Monitor unit	778±122	463±45	*<0.0001*
Treatment time (s)	225.6±62.0	188.8±0.8	0.0929

p–values in italics are statistically significant.

Table 3. Dose-volumetric comparison of intensity-modulated radiation therapy (IMRT) and RapidArc® [RA; (Varian Medical Systems, Palo Alto, CA)] in patients with primary liver tumour (Group B)

Variable	Mean ± standard deviation		*p*–value
	IMRT	RA	
Conformity index	1.1±0.05	1.0±0.05	*<0.0001*
Mean whole liver dose (Gy)	23.1±7.4	23.7±7.6	0.0526
Mean non-target liver dose (Gy)	16.7±6.7	17.4±7.0	0.0568
Max spinal cord dose (Gy)	33.9±7.2	27.7±7.2	*0.0008*
$V_{30\ Gy}$ of whole liver (%)	33.3±14.0	32.9±14.2	0.4597
$V_{30\ Gy}$za of non-target liver (%)	19.0±11.8	18.5±12.3	0.4268
$V_{35\ Gy}$ of duodenum (%)	7.1±9.9	6.6±8.9	0.5518
$V_{35\ Gy}$ of stomach (%)	12.9±15.9	9.9±11.8	0.0762
$V_{20\ Gy}$ of kidney (%)	11.9±13.7	7.3±9.5	*0.0124*
Right kidney (%)	18.7±25.0	12.7±17.3	0.0836
Left kidney (%)	5.0±9.4	1.9±4.8	0.0848
Monitor unit	791±138	457±77	*<0.0001*
Treatment time (s)	198.6±12.8	188.9±0.5	*0.0359*

p–values in italics are statistically significant.

respectively). In Group B, in contrast, neither mean doses nor $V_{30\ Gy}$ of the whole liver and non-target liver significantly differed between the two plans. As for non-liver OARs, $V_{35\ Gy}$ of duodenum was decreased with RA *vs* IMRT in group A (17.9% *vs* 20.9%, $p=0.0058$), while $V_{20\ Gy}$ of kidneys was decreased in group B (7.3% *vs* 11.9%, $p=0.0124$). When divided into right and left kidneys, the statistical significance of difference in $V_{20\ Gy}$ of each kidney in Group B was marginal, but a similar trend of lowered value with RA was observed in each kidney. $V_{35\ Gy}$ of stomach was decreased with RA in both groups, but statistical significance was not reached. Maximal dose to the spinal cord and total monitor unit were significantly lower in RA, regardless of the group. In terms of treatment time, RA was more efficient than IMRT; statistical significance was reached in Group B, but marginal in Group A. The average DVHs of RA *vs* IMRT for (a) whole liver, (b) non-target liver, (c) stomach, (d) duodenum, (e) kidney and (f) spinal cord are shown in Figures 1 and 2. Also, the dose distributions of RA *vs* IMRT for a selected patient in the Groups A and B are compared in Figures 3 and 4, respectively.

Discussion

As mentioned earlier, there are several dosimetric studies evaluating the benefit of IMRT for HCC. Cheng et al [3] compared IMRT *vs* three-dimensional conformal radiotherapy for HCC, and reported that IMRT resulted in an increased mean liver dose, while reducing (or at least achieving similar) non-liver OAR sparing, such as spinal cord, kidneys or stomach. Eccles et al [4] compared IMRT *vs* three-dimensional conformal radiotherapy in the hypofractionation setting, and tried a dose escalation using IMRT. Although dose escalation was feasible only in 35% of patients, a significant increase in the minimal dose to 93% of the PTV was observed with IMRT for all patients without increase in the doses to non-liver OARs such as stomach, duodenum and spinal cord. They also evaluated the implication of the PTV location on the dose-volumetric results, and observed that cases with a PTV overlapping or directly adjacent to non-liver OARs had a greater advantage with IMRT than ''non-overlapping'' cases in which the liver itself was the OAR.

In this study, we compared two different IMRT techniques: RA *vs* static field IMRT. In general, RA tended to be more effective in the sparing of non-liver OARs such as duodenum, kidney and spinal cord. However, the dose-volumetric results of RA *vs* IMRT were different according to the target location within the liver. Our patients were divided into two groups by the PTV location. Group A consisted of 10 patients with portal vein tumour thrombosis, and their PTVs were located in the central portion of the liver. In contrast, Group B consisted of 10 patients with primary liver tumour, and their PTVs were located in the peripheral portion of the liver, either in the right lobe adjacent to the right kidney ($n=4$) or left lobe adjacent to the stomach ($n=6$). As a result, $V_{35\ Gy}$ of duodenum, which is located adjacent to the central portion of the liver, was decreased with RA in group A, while $V_{20\ Gy}$ of kidneys, which was located adjacent to peripheral portion of the liver (especially, right kidney), was decreased with RA in group B. From these observations, it can be summarised that adjacent OARs were more effectively spared with RA.

However, the increased mean liver dose in group A with RA should not be overlooked. As for the implication of mean liver dose in the development of radiation-induced liver disease, however, there are several conflicting reports. Some investigators suggested mean liver dose was associated with the hepatic toxicity [9, 10], while others did not [11, 12]. Cheng et al [3] reported increased mean liver dose but reduced normal tissue complication probability of liver with IMRT. Although the delivery of beams during gantry rotation did increase mean liver dose the difference was balanced by the decreasing $V_{30\ Gy}$ of the liver, and this dose–volume effect on the development of radiation-induced liver disease has not been evaluated (and needs to be elucidated in the clinical setting).

Despite the statistical significance, however, the absolute difference in dose-volumetric results (including non-liver OAR sparing, increased mean liver dose and decreased $V_{30\ Gy}$ of liver) between IMRT and RA plans is quite small. In contrast, there was

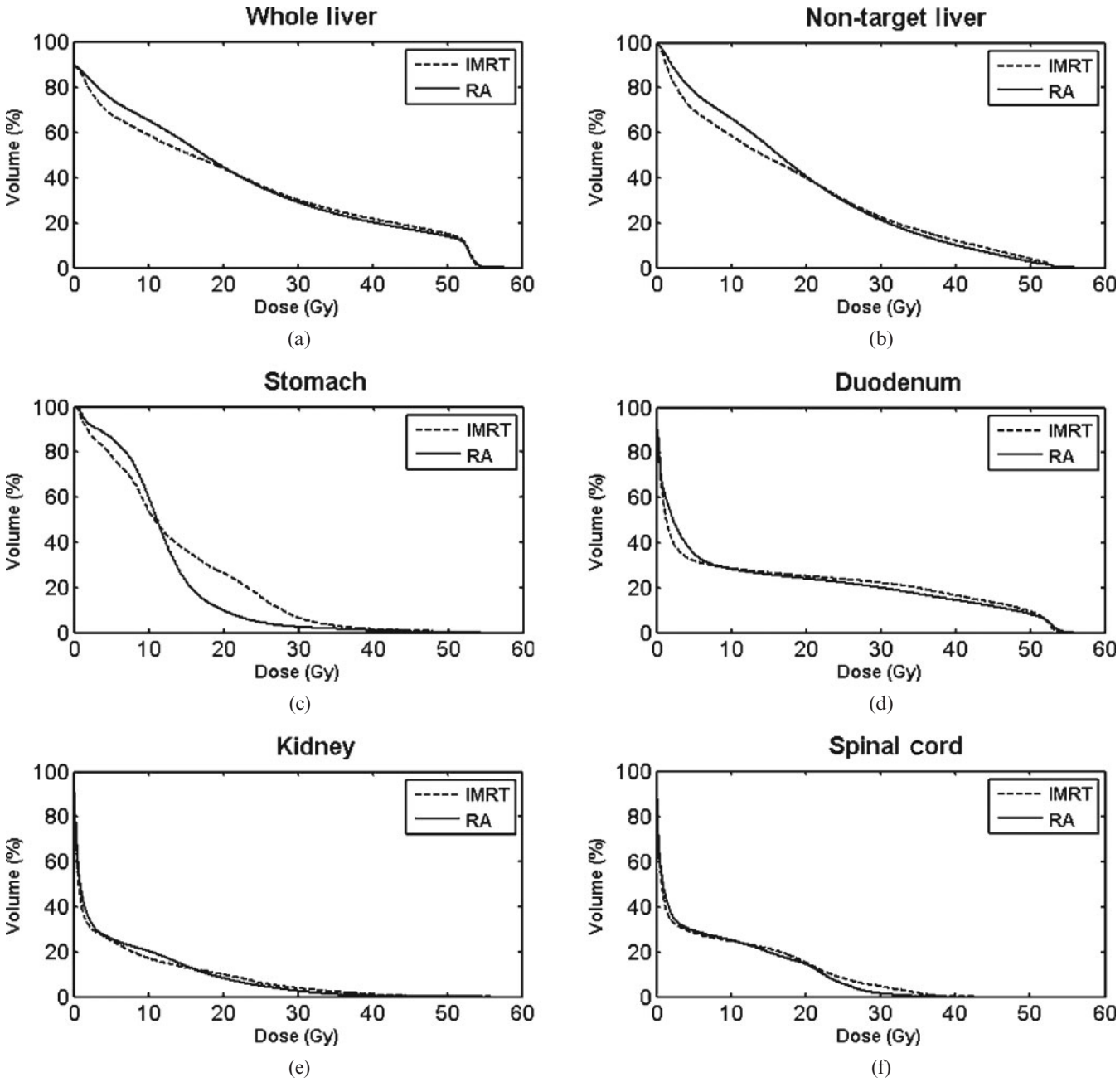

Figure 1. Average dose–volume histograms of RapidArc® (RA; Varian Medical Systems, Palo Alto, CA) *vs* intensity-modulated radiation therapy (IMRT) for (a) the whole liver, (b) non-target liver, (c) stomach, (d) duodenum, (e) kidney and (f) spinal cord (Group A).

only a trend towards decreased $V_{35\,Gy}$ of stomach with RA in both groups, but the mean DVHs suggest that there may be much reduction of irradiated stomach volume in the lower dose range of about 20 Gy. Recently, Kim et al [13] reported that $V_{35\,Gy}$ was the most significant factor predicting gastroduodenal complications in HCC patients treated with radiotherapy, but $V_{5\,Gy}$, $V_{10\,Gy}$, $V_{15\,Gy}$, $V_{20\,Gy}$, $V_{25\,Gy}$ and $V_{30\,Gy}$ were also associated with the toxicity. Moreover, the dose-volumetric improvement in the lower dose range may be meaningful in the stereotactic body radiotherapy (SBRT) setting. Murphy et al [14] analysed the dosimetric determinants of duodenal toxicity in single-fraction SBRT for pancreatic cancer, and reported that $V_{10\,Gy}$, $V_{15\,Gy}$, $V_{20\,Gy}$ and $V_{25\,Gy}$ were significantly correlated with duodenal toxicity. Further investigation is needed to confirm the dose–volume relationship of gastric and/or duodenal toxicity, and for evaluating the clinical implication of the improved dose-volumetric results with RA shown in our study.

Lastly, treatment efficiency is an important factor to be considered in the treatment. In our study, regardless of the group, total monitor unit was much smaller in RA plans. Treatment time was also reduced with RA, but the magnitude of reduction was less than that of the previous reports from other treatment sites [6, 15, 16]. This might be due to the employed techniques of RA and IMRT in our study. 2.5 arcs were employed to maximise the benefit of RA, whereas the number of fields of IMRT was limited to five to save the liver as much as possible. Despite this, however, the treatment time of RA was

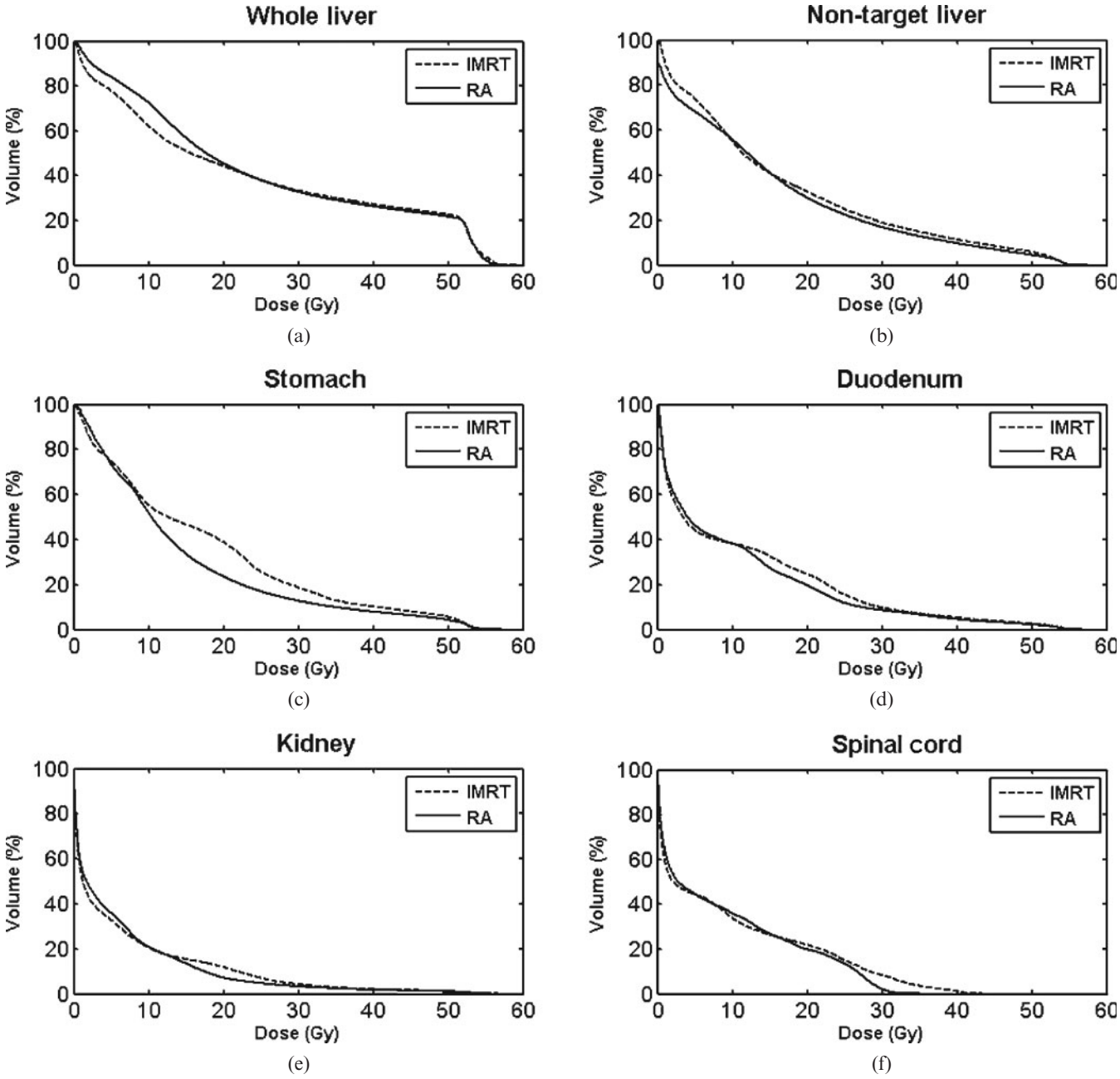

Figure 2. Average dose–volume histograms of RapidArc® (RA; Varian Medical Systems, Palo Alto, CA) *vs* intensity-modulated radiation therapy (IMRT) for (a) the whole liver, (b) non-target liver, (c) stomach, (d) duodenum, (e) kidney and (f) spinal cord (Group B).

still shorter than that of IMRT. Plan efficiency can also be improved with RA, because the dose distribution of static field IMRT is more dependent on the beam angle, and the selection of the optimal beam angle relies on the experience of the planning dosimetrist or physicist.

There are concerns that the organ motion during respiration can lead to the under-dosed area within the target. Some may argue that the hollow viscus (such as duodenum and stomach) can move unpredictably, even regardless of respiration. However, we delineated the internal target volume based on three-phase CT including free breathing, full inhalation and full exhalation. Moreover, this study is a comparative planning study using the same data set, and therefore the comparison of the treatment plans between RA and IMRT was not affected by the organ motion. There are several reports evaluating the interplay effect between multileaf collimator motion and organ motion in the treatment using RA. Some investigators noted that the interplay effect of RA was minimal compared with IMRT [17], whereas others did not [18]. This issue is beyond the scope of discussion in our study, but further studies are needed to minimise the error in the delivered dose during treatment.

Conclusion

The dose-volumetric results of RA *vs* IMRT were different by the different target location within the liver. In general, RA tended to be more effective in sparing non-liver OARs such as duodenum, kidney and spinal

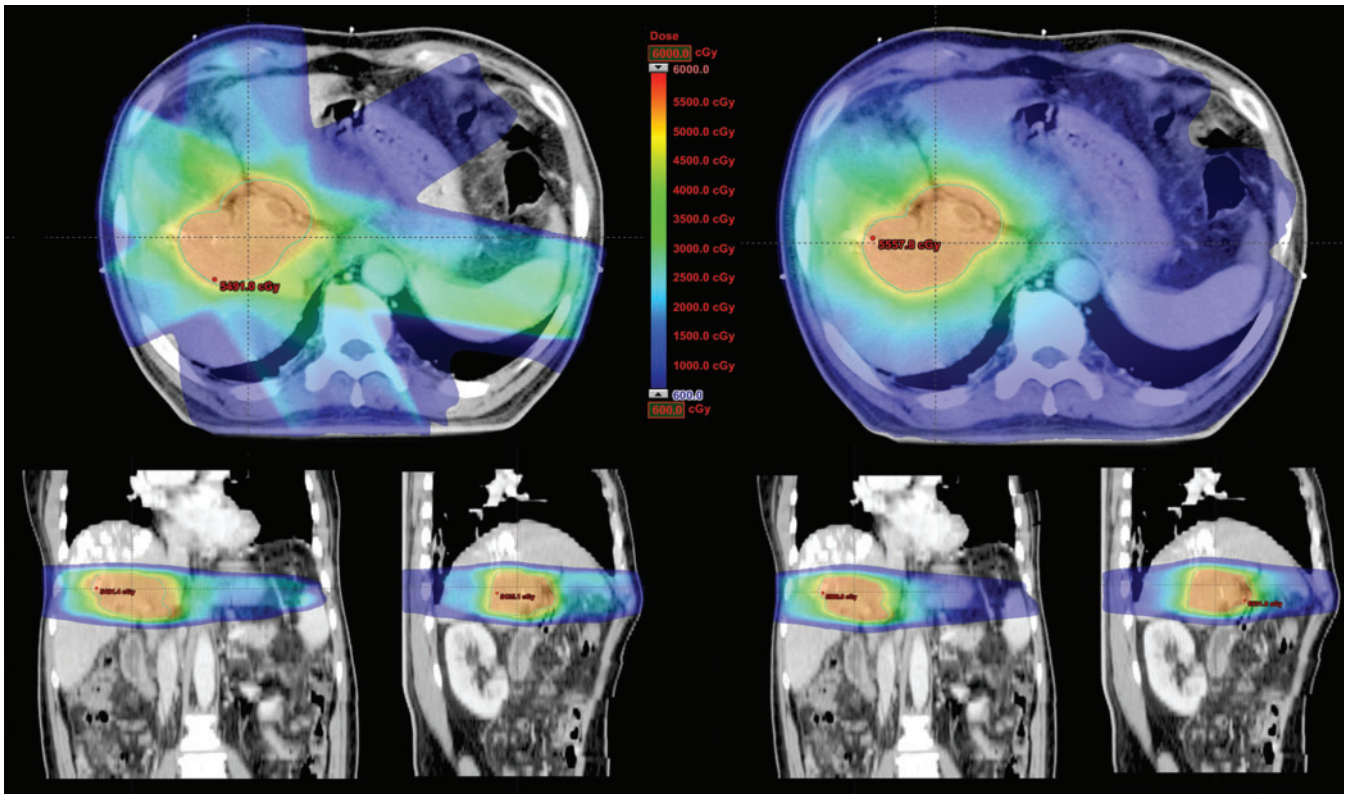

Figure 3. Dose distributions of RapidArc® (Varian Medical Systems, Palo Alto, CA) *vs* intensity-modulated radiation therapy for one patient in Group A.

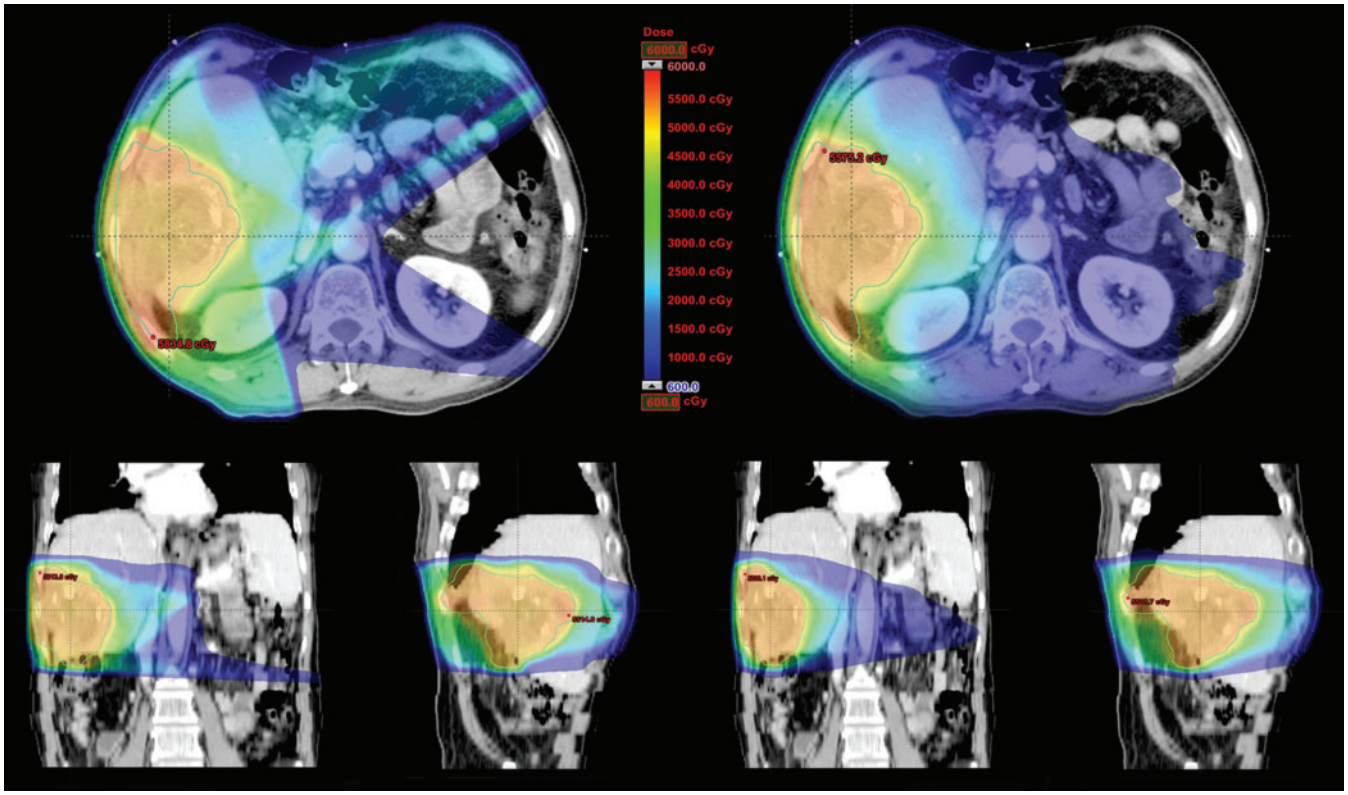

Figure 4. Dose distributions of RapidArc® (Varian Medical Systems, Palo Alto, CA) *vs* intensity-modulated radiation therapy for one patient in Group B.

cord. Moreover, RA was more efficient in the treatment delivery compared with IMRT in terms of total monitor unit used.

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