

Four-dimensional CT-based evaluation of volumetric modulated arc therapy for abdominal lymph node metastasis from hepatocellular carcinoma

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This study aimed to identify the potential benefits and limitations of a new volumetric modulated arc therapy (VMAT) planning system in Monaco, compared with conventional intensity-modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3DCRT). Four-dimensional CT scans of 13 patients with abdominal lymph node metastasis from hepatocellular carcinoma were selected. Internal target volume was defined as the combined volume of clinical target volumes (CTVs) in the multiple 4DCT phases. Dose prescription was set to 45 Gy for the planning target volume (PTV) in daily 3.0-Gy fractions. The PTV dose coverage, organs at risk (OAR) doses, delivery parameters and treatment accuracy were assessed. Compared with 3DCRT, both VMAT and IMRT provided a systematic improvement in PTV coverage and homogeneity. Planning objectives were not fulfilled for the right kidney, in which the 3DCRT plans exceeded the dose constraints in two patients. Equivalent target coverage and sparing of OARs were achieved with VMAT compared with IMRT. The number of MU/fraction was 462 ± 68 (3DCRT), 564 ± 105 (IMRT) and 601 ± 134 (VMAT), respectively. Effective treatment times were as follows: 1.8 ± 0.2 min (3DCRT), 6.1 ± 1.5 min (IMRT) and 4.8 ± 1.0 min (VMAT). This study suggests that the VMAT plans generated in Monaco improved delivery efficiency for equivalent dosimetric quality to IMRT, and were superior to 3DCRT in target coverage and sparing of most OARs. However, the superiority of VMAT over IMRT in delivery efficiency is limited.

Keywords: liver radiotherapy; volumetric modulated arc therapy; four-dimensional computed tomography (4DCT); intensity-modulated radiotherapy

INTRODUCTION

The efficacy of radiotherapy for the management of abdominal lymph node (LN) metastasis from hepatocellular carcinoma (HCC) has been proven, with excellent overall response rates of 65.5–96.8%, and a median survival ranging from 7 to 13 months [1–3]. Although radiotherapy is an effective management option for abdominal LN metastasis, the gastrointestinal tract is often included in the treatment, which can result in severe complications [1–3]. Thus, the challenge inherent in using advanced radiation techniques is how to improve the degree of conformal avoidance.

Previous studies have shown that intensity-modulated radiotherapy (IMRT) produces highly conformal dose distributions, and is of benefit to liver lesions adjacent to serial functioning normal tissues, compared with three-dimensional conformal radiotherapy (3DCRT) [4, 5]. Volumetric modulated arc therapy (VMAT) is a novel extension of the standard IMRT technique, allowing dose delivery with simultaneously varying gantry speed, multileaf collimator (MLC) shape and dose rate [6]. The technique has been previously investigated in multiple tumor sites, and has shown similar or better plan quality and much higher treatment efficiency than standard IMRT [6–10]. Currently, most VMAT studies have been generated using

RapidArcTM (Varian Medical Systems, Palo Alto, CA), Pinnacle³ SmartArcTM (Philips Healthcare, Madison, WI), and OncentraTM MasterPlan (Nucletron BV, Veenendaal, the Netherlands) [6–10]. A new VMAT treatment planning tool with a Monte Carlo algorithm for the dose calculation was clinically released in Monaco (CMS, Elekta, Crawley, UK) in March 2010. The quality of a VMAT plan is highly dependent on the actual optimization algorithm implemented in the treatment planning system (TPS), and we therefore believed that it was important to investigate the clinical applicability of the recent Monaco installation at our institute.

The aim of this study was to investigate the potential benefits and limitations of this new VMAT treatment plan compared with IMRT and 3DCRT for patients with abdominal LN metastasis from HCC.

MATERIALS AND METHODS

Patient selection and contouring

Four-dimensional computed tomography (4DCT) scans of 13 patients with abdominal LN metastasis from HCC who were treated with 3DCRT were selected for this comparative analysis. Patient and tumor characteristics are listed in Table 1.

Patients were immobilized with vacuum bags in the supine position with their arms raised above their head during simulation. Contrast-enhanced 4DCT scanning was carried out during uncoached quiet breathing with a 2.5-mm slice thickness on a 16-slice positron emission tomography (PET)/CT (GE Medical Systems, Waukesha, WI, USA), as has been previously described [11]. Following 4DCT scanning, images were sorted into 10 phases based on the temporal correlation between surface motion and data acquisition on Advantage Workstation 4.2 (GE Medical Systems).

Gross tumor volumes (GTVs) and clinical target volumes (CTVs) were manually contoured on all 10 phases of the 4DCT scan by a single clinician. GTV represented the LN metastasis lesion visualized on the CT images, and CTV was defined as GTV plus an isotropic margin of 0.3 cm. The internal target volume (ITV) was defined as the combined volume of CTVs in multiple 4DCT phases. To account for residual intrafractional organ motion, interfractional motion variability and patient setup errors, an isotropic margin of 0.6 cm was added to the ITV to generate the planning target volume (PTV), which is typically used for abdominal malignancies at our institute. Organs at risk (OARs) including the liver, kidney, stomach, small intestine, spleen and spinal cord, were contoured on the 20% CT image (mid-exhalation) for dose calculations. Normal liver volume was defined as the total liver volume minus the PTV.

Planning objectives and techniques

The dose prescription was set to 45 Gy for the PTV in daily 3.0-Gy fractions. Normalization was set to the PTV

mean dose in the optimization and evaluation processes. For PTVs, plans aimed to achieve a minimum dose greater than 90% of the prescribed dose and a maximum lower than 110%. Planning objectives for OARs were defined as follows: liver, mean dose <23 Gy, $V_{30\text{Gy}} <30\%$, $V_{20\text{Gy}} <50\%$; kidney, mean dose <20 Gy; stomach, $V_{30\text{Gy}} <40\%$; small intestine, maximum dose <50 Gy; spleen, $V_{30\text{Gy}} <30\%$; and spinal cord, maximum dose <40 Gy.

For each patient, three treatment plans were calculated: 3DCRT, IMRT and VMAT. The same isocenter of the three plans was used, which was positioned at the geometric center of the PTV. All plans were designed and optimized for an Elekta Synergy accelerator (MLCi2 80 leaves, 1 cm MLC) using 8-MV photons.

3DCRT

3DCRT plans were generated using the Pinnacle TPS (Philips ADAC Pinnacle³ 8.0 m). Three to five coplanar beams with different wedge angles were applied and a collapsed cone algorithm was used for dose calculations. Beam directions and weights were manually optimized in relation to the location of the target and the OARs.

IMRT

As the target was on the right side of the abdominal cavity, MLC-based step-and-shoot IMRT was developed with seven coplanar fields selecting the best geometry for each patient, excluding direct entrance through the left kidney. For both IMRT and VMAT, the dose calculations and optimizations were performed using the Monaco TPS (Version 3.0), offering equivalent uniform dose-based biological optimization combined with physical and radiobiological cost functions. Monaco IMRT uses a two-stage process for optimizing dose distributions. The first stage is performed on a Pencil Beam dose calculation algorithm to obtain the ideal modulated fluence. In stage two, the segments are optimized on the direct machine parameters using the Monte Carlo algorithm [12].

VMAT

Planning for VMAT follows the same workflow as planning for standard IMRT in Monaco. A partial arc range of 230° was manually selected to spare the left kidney. The VMAT technique uses a simultaneous variation of gantry rotational speed, MLC leaf positions and dose rate to optimize the dose distribution. The maximal leaf speed for the Elekta linac was 2.4 cm/s, and the maximum gantry speed was 6.0°/s. The maximum dose rate was set to 700 MU/min; the VMAT algorithm modulated the dose rate in steps of 50% to a minimum fluence rate of 11 MU/min.

Both the IMRT and the VMAT plans were optimized using identical planning objectives by the same experienced physicist, in order to minimize inter-observer variations.

Table 1. Patient and tumor characteristics

No.	Sex	Age (years)	LN location	GTV (cc)	PTV (cc)	LN mobility in CC (mm)
1	Male	53	Portal, peripancreatic, paraaortic	104.9	318.9	7.5
2	Male	58	Peripancreatic, paraaortic	224.2	628.9	2.0
3	Male	54	Peripancreatic, paraaortic	128.8	283.9	3.2
4	Female	65	Portal, peripancreatic	27.7	152.3	10.0
5	Male	53	Paraaortic	25.2	193.2	8.8
6	Female	45	Portal	17.3	188.4	5.2
7	Male	59	Portal, peripancreatic, paraaortic	193.0	414.6	4.8
8	Male	52	Paraaortic	17.9	189.7	7.6
9	Female	58	Paraaortic	15.7	150.7	5.7
10	Male	44	Portal, peripancreatic	64.5	357.1	7.5
11	Male	53	Portal, peripancreatic	49.6	347.5	8.0
12	Male	45	Portal, peripancreatic, paraaortic	203.0	437.5	4.0
13	Male	43	Portal, peripancreatic, paraaortic	234.2	555.0	9.0

GTV, gross tumor volume; PTV, planning target volume; LN, lymph node; CC, cranial–caudal direction.

Evaluation of treatment plans

The dose distributions were evaluated quantitatively using dose–volume histograms (DVH) for each plan. For PTVs, the values of $D_{1\%}$ (dose received by 1% of the volume) and $D_{99\%}$ were defined as metrics for maximum and minimum doses and reported. The $V_{95\%}$ (the volume receiving $\geq 95\%$ of the prescribed dose), $V_{100\%}$ and $V_{107\%}$ were also reported. The homogeneity index was expressed in terms of $D_{5\%} - D_{95\%}$, as defined by Bignardi *et al.* [7]. The conformity index ($CI_{95\%}$) was defined as the ratio between the patient's volume receiving $\geq 95\%$ of the prescribed dose and the volume of the PTV. Both $CI_{80\%}$ and $CI_{60\%}$ were also reported in order to evaluate the dose gradient. The average cumulative DVHs for PTV and OARs were built from individual DVHs, averaging the corresponding volumes over the patient's cohort for each dose bin of 0.01 Gy. In addition, the time required for planning was recorded, measured from the start of the optimization until the end of the final dose calculation.

Regarding the efficiency of treatment delivery, the effective treatment time and the number of MU/fraction were analyzed. Delivery times were measured at the linac during simulated delivery, defined as beam-on time plus the time needed to reset the system between beams. To assess the delivery quality and agreement between the calculations and treatment, dosimetric verification of the IMRT and VMAT plans were determined by comparison with measured dose values performed with the Delta4 phantom (ScandiDos, Uppsala, Sweden), as described by Bedford *et al.* [13]. The gamma evaluation criteria were $\pm 3\%$ of 3 Gy and 3 mm of the distance criterion.

Statistical analysis

Data were analyzed using the one-way analysis of variance (ANOVA) by SPSS 13.0 software (SPSS, Chicago, IL, USA). Differences were considered to be significant if the two-tailed P -value was less than 0.05.

RESULTS

Typical dose distributions are shown in Fig. 1 for axial and coronal views. Fig. 2 presents the average DVH for PTVs and OARs. Tables 2 and 3 report the numeric findings from the DVH analysis of the PTVs and OARs, respectively.

Target coverage and dose homogeneity

As can be seen in Table 2, for the PTV, both the VMAT and the IMRT plans provided a systematic improvement that was statistically significant for dose coverage and homogeneity, compared with the 3DCRT plans. The conformity of the dose distribution was similar for the three plans, whereas VMAT and IMRT showed a steeper dose gradient compared with 3DCRT (Table 2 and Fig. 2). In addition, the target coverage and homogeneity were similar for the VMAT and IMRT plans ($P > 0.05$).

OARs

Both the VMAT and the IMRT plans were shown to fulfil the planning objectives. On the other hand, the planning objective was not fulfilled for the right kidney of two patients in the 3DCRT plans. Compared with 3DCRT, VMAT and IMRT showed a superior sparing for most OARs, including the left kidney, right kidney, spleen, stomach and spinal cord (Table 3). Conversely, the mean

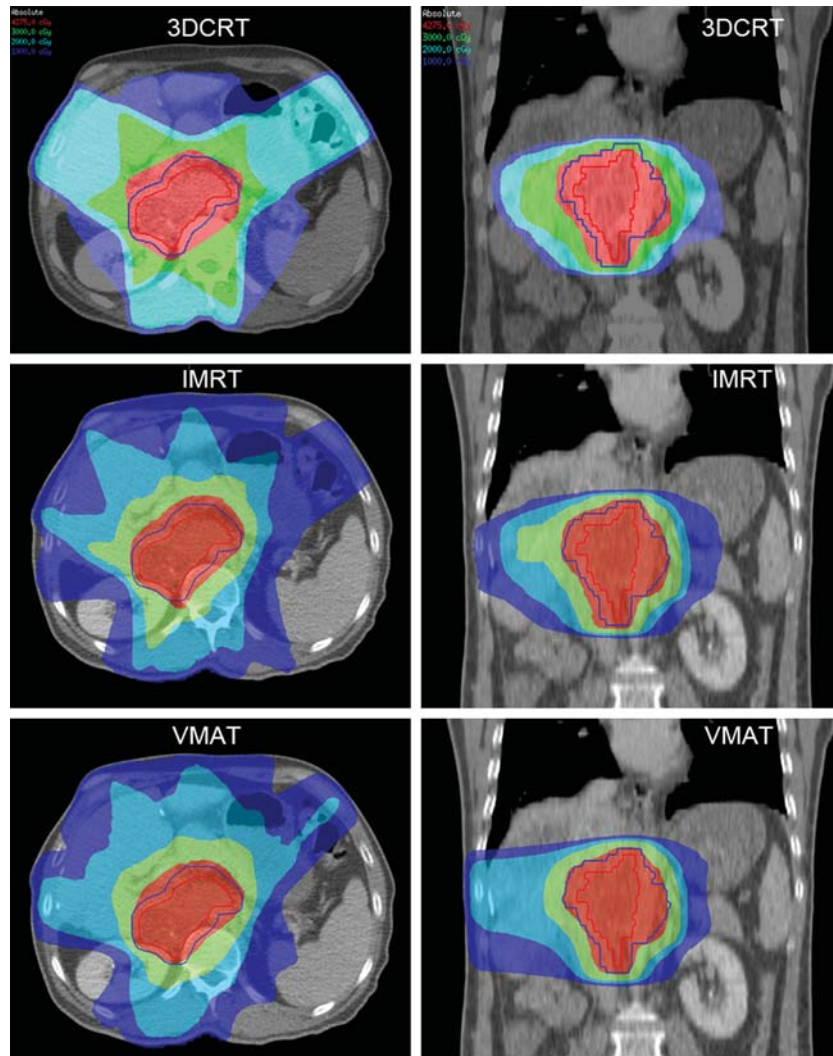


Fig. 1. (Pt. No. 3) typical dose distribution in axial and coronal views. Color wash is cut between 10.00 Gy and 42.75 Gy. The red contour and blue contour represent the GTV and PTV, respectively.

dose to the liver was lower with 3DCRT than with IMRT or VMAT. In addition, VMAT allowed minor improvements with no significant difference in sparing of the liver, right kidney and small intestine, compared with IMRT.

Delivery parameters and accuracy

The average number of MU/fraction was 462 ± 68 for 3DCRT, 564 ± 105 for IMRT, and 601 ± 134 for VMAT ($P=0.005$). A slightly higher number of MU for VMAT than for IMRT was observed, with an average increase of 6.6% ($P=0.374$). The average effective treatment times were as follows: 1.8 ± 0.2 min for 3DCRT, 6.1 ± 1.5 min for IMRT and 4.8 ± 1.0 min for VMAT ($P<0.001$). Compared WITH IMRT, the VMAT delivery times were found to be on average 21.3% faster.

The times required for optimization and dose calculation were 2.6 ± 0.7 min for 3DCRT, 22.3 ± 3.9 min for IMRT

and 23.1 ± 4.0 min for VMAT ($P<0.001$). Both the IMRT and VMAT techniques presented high accuracy in dose delivery. The passing rate of the gamma evaluation was $98.9 \pm 0.8\%$ for IMRT and $99.2 \pm 0.4\%$ for VMAT ($P=0.51$).

DISCUSSION

The number of studies on treatment planning and dosimetric comparisons of VMAT with existing radiation techniques for abdominal lesions has been limited to date. In this study, we systematically compared VMAT, step-and-shoot IMRT and the 3D conformal technique in patients with abdominal LN metastasis from HCC.

As expected, IMRT achieved a clear improvement on target coverage compared with that achieved by conformal irradiation in this study. Both VMAT and IMRT plans showed an equivalent degree of target coverage, conformity

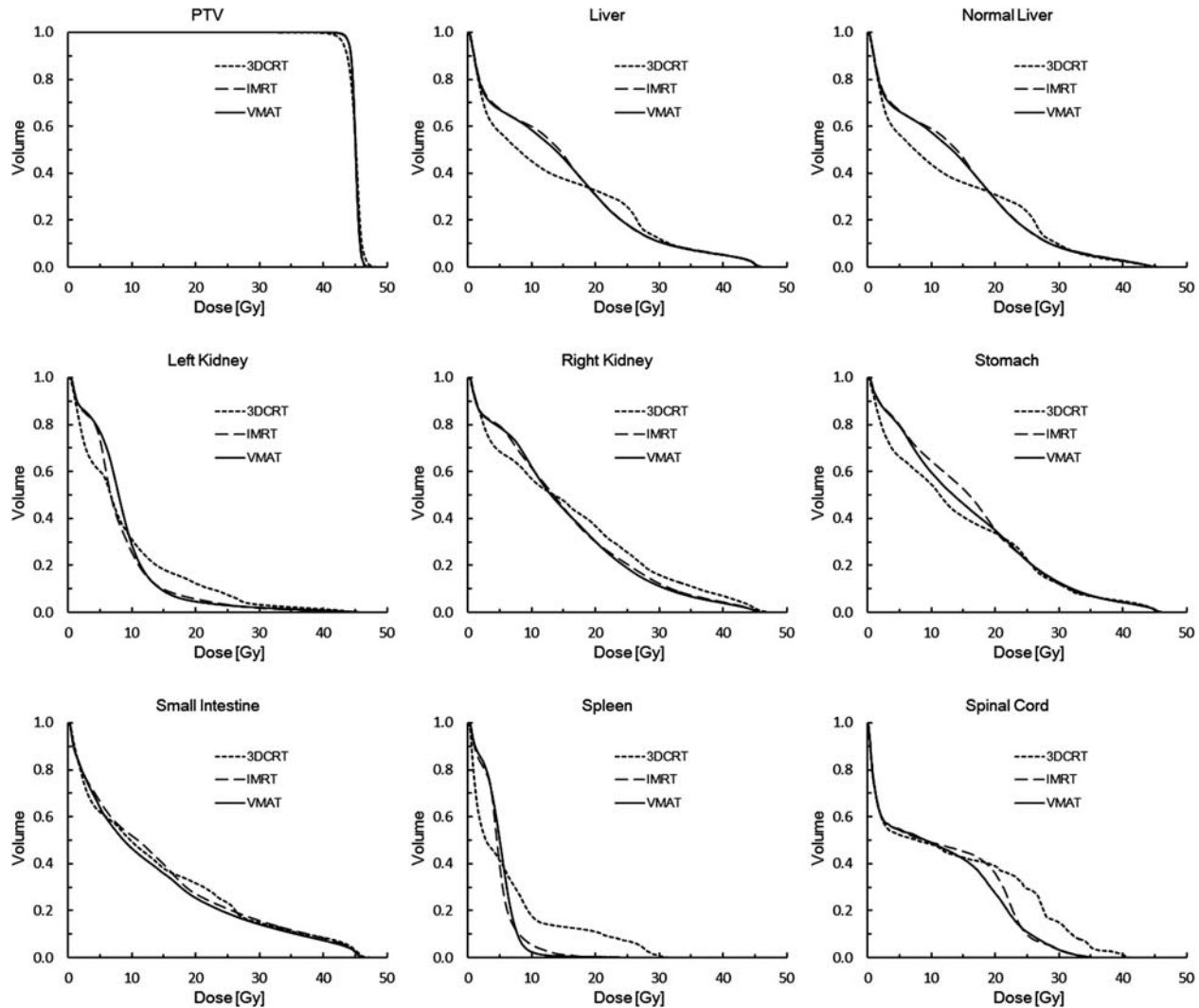


Fig. 2. Average dose–volume histograms for PTV and OARs

and homogeneity, consistent with that reported by other groups [7–10]. With respect to OARs, the dose delivered to normal tissues was similar or slightly lower for VMAT than for IMRT. Both VMAT and IMRT showed a superior sparing of the kidney, spleen, stomach and spinal cord compared with 3DCRT. The decrease in the dose delivered to the stomach is important, as gastrointestinal complications are a frequent side-effect of radiotherapy for abdominal malignancy [1–3]. However, the superiority of VMAT/IMRT for the small intestine was not observed in our study. In terms of the mean dose delivered to the OARs, Bignardi *et al.* [7] concluded that IMRT/VMAT facilitated minor improvements for the liver compared with 3DCRT, a finding inconsistent with our data. However, it should be noted that the 3DCRT plans were designed using more fixed beams in their study (four to eight) than in ours (three to five). Thus, the difference in the mean dose

delivered to the liver between the two studies mainly reflects differences in the design of the 3DCRT plans.

Previous studies have generally shown that VMAT generated by RapidArc or SmartArc is able to reduce the MU/fraction by about 26–60% compared with IMRT [6–10]. Conversely, a minor increase in the MU/fraction (6.6%) was observed when changing from IMRT to VMAT in our study. Table 4 presents a synopsis of delivery parameters from recent reports that addressed the role of VMAT for the treatment of abdominal tumors, compared with the findings of the current study. It is clear that the MU/Gy in our IMRT plans was much less than that reported in other studies, although the target volumes, planning objectives and dose per fraction were different in these studies [7, 14, 15]. In addition, the MU/Gy in our VMAT plans was within the wide range that has been previously reported [7, 14, 15]. Therefore the difference in the MU increase is

Table 2. Summary of averaged dosimetric results for PTV

Item	3DCRT	IMRT	VMAT	P
PTV: 324.4 ± 153.8 cc				
Mean (Gy)	45.0 ± 0.0	45.0 ± 0.0	45.0 ± 0.0	
D _{1%} (Gy)	46.7 ± 0.8	46.3 ± 0.1	46.5 ± 0.5	
D _{99%} (Gy)	41.5 ± 1.4	43.3 ± 0.2	43.1 ± 0.4	a, b
V _{95%} (%)	97.0 ± 1.3	99.6 ± 0.2	99.4 ± 0.6	a, b
V _{100%} (%)	57.5 ± 8.9	56.0 ± 0.9	55.3 ± 2.5	
V _{107%} (%)	0.1 ± 0.4	0.0 ± 0.0	0.0 ± 0.0	
HI (Gy)	3.1 ± 0.9	1.9 ± 0.1	1.9 ± 0.6	a, b
CI _{95%} (%)	1.4 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	
CI _{80%} (%)	2.1 ± 0.3	2.0 ± 0.2	2.0 ± 0.2	
CI _{60%} (%)	4.1 ± 0.9	3.4 ± 0.4	3.3 ± 0.3	a, b

PTV, planning target volume; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy; HI, homogeneity index; CI, conformity index; Dx%, dose received by x% of volume; Vx%, volume receiving at least x% of prescribed dose.

Statistical significance with $P < 0.05$, a = 3DCRT vs. IMRT, b = 3DCRT vs. VMAT, c = IMRT vs. VMAT.

mainly related to the number of MU in the IMRT plans, and not to the number of MU in the VMAT plans. The number of MU is highly dependent on the type of optimization algorithm and the techniques used during IMRT planning. Rather than the dynamic sliding window method performed in the Eclipse planning system, the step-and-shoot IMRT optimization with fewer segments was used in the Monaco TPS. This may be the main reason for the reduction in MU in the IMRT plans in the current study.

Many reports have demonstrated that the major advantage of VMAT over IMRT is the higher delivery efficiency combined with a reduction in treatment time of approximately 35–61% [6–10]. Nevertheless, only a modest reduction (21.3%) in delivery time was observed in our study. As can be seen in Table 4, the average treatment time in the current study is longer than that reported when delivering VMAT using RapidArc on Varian accelerators [7, 14, 15]. This difference is mainly due to the binned dose rate mode on current Elekta accelerators. In contrast to the continuous dose rate shifts on Varian accelerators, only seven fixed dose levels are available on Elekta accelerators, with each level half the dose rate of the next higher level. By upgrading to the next version of the accelerator-controlling system, a faster delivery should be possible. In addition, IMRT plans generated by Monaco could automatically integrate the multiple beams into a combined one, thus reducing the time required to move the gantry between different fields manually (approximately 1 min for seven fields).

Table 3. Summary of dosimetric results for OARs

Item	3DCRT	IMRT	VMAT	P
Liver: 1414.8 ± 421.1 cc				
Mean (Gy)	13.4 ± 4.9	14.6 ± 4.6	14.4 ± 4.3	a, b
V _{30Gy} (%)	12.2 ± 5.3	11.0 ± 5.0	10.8 ± 4.8	
V _{20Gy} (%)	32.5 ± 14.4	30.4 ± 13.0	30.1 ± 12.1	
Normal liver: 1377.0 ± 420.5 cc				
Mean (Gy)	12.6 ± 4.6	13.8 ± 4.3	13.6 ± 4.0	a, b
V _{30Gy} (%)	9.7 ± 4.7	8.7 ± 3.8	8.5 ± 3.6	
V _{20Gy} (%)	30.9 ± 14.3	28.9 ± 12.5	28.6 ± 11.6	
Left kidney: 201.7 ± 43.7 cc				
Mean (Gy)	9.0 ± 4.2	8.2 ± 3.7	8.6 ± 3.3	
V _{20Gy} (%)	12.3 ± 16.5	5.7 ± 9.6	4.5 ± 8.9	a, b
Right kidney: 186.0 ± 39.9 cc				
Mean (Gy)	15.9 ± 6.5	15.3 ± 3.0	15.0 ± 3.6	
V _{20Gy} (%)	36.8 ± 20.1	30.1 ± 19.2	30.0 ± 18.5	a, b
Stomach: 366.4 ± 192.1 cc				
V _{40Gy} (%)	4.8 ± 7.7	4.1 ± 7.4	4.0 ± 7.3	
V _{30Gy} (%)	12.2 ± 12.7	12.1 ± 14.1	12.1 ± 15.0	
Small intestine: 451.7 ± 297.4 cc				
Max (Gy)	45.3 ± 2.8	45.2 ± 2.3	45.2 ± 2.7	
V _{15Gy} (cc)	148.2 ± 93.9	160.4 ± 93.9	146.6 ± 83.5	
V _{45Gy} (cc)	11.3 ± 8.9	8.5 ± 4.9	8.2 ± 5.0	
Spleen: 311.1 ± 293.7 cc				
Mean (Gy)	6.5 ± 5.0	4.7 ± 2.2	4.9 ± 1.7	a, b
Spinal cord: 41.2 ± 10.7 cc				
Max (Gy)	29.9 ± 6.4	27.3 ± 4.2	27.2 ± 4.7	

Abbreviations as in Table 2.

Therefore, the difference in the treatment time reduction is partly related to the IMRT delivery time.

Dobler *et al.* [16] reported that a drawback for VMAT planning with OncentraTM MasterPlan, as compared with IMRT is the increased calculation time, which is increased by a factor of 5.0 to 6.8. However, VMAT planning has the potential to produce a similar plan quality, and required a similar planning time compared with IMRT in our study. Thus, VMAT planning generated by Monaco has no impact on the workload or on the availability of the TPS.

It is also important to discuss the role of respiratory motion, which is typically included in radiotherapy treatment planning for abdominal tumors. It has been reported that using 4DCT images to determine individualized ITV is the ideal way to account for organ motion when treating liver cancer [11]. Our study revealed that the average breathing movement of abdominal LNs was 6.4 ± 2.4 mm in the cranial–caudal direction. When considering breathing

Table 4. Synopsis of delivery parameters from recent studies for VMAT in abdominal malignancies

Authors	Tumor site	Dose per fraction (Gy)	TPS	IMRT			VMAT		
				MU/fraction	MU/Gy	Treatment time (min)	MU/fraction	MU/Gy	Treatment time (min)
Bignardi <i>et al.</i> [7]	Abdominal LN	7.5	Eclipse	2583 ± 699	344 ± 93	10.6 ± 1.2	2186 ± 211	291 ± 28	3.7 ± 0.4
Eppinga <i>et al.</i> [14]	Pancreas	1.8	Eclipse	800 ± 209	444 ± 116	8.0	561 ± 95	312 ± 36	< 3.0
Shaffer <i>et al.</i> [15]	Retroperitoneum	1.8	Eclipse	665 ± 215	369 ± 119	4.0 ± 1.1	325 ± 71	181 ± 39	1.3 ± 0.0
Present study	Abdominal LN	3.0	Monaco	564 ± 105	188 ± 35	6.1 ± 1.5	601 ± 134	200 ± 45	4.8 ± 1.0

TPS, treatment planning system; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy; MU, monitor unit; LN, lymph node.

motion, the use of motion management, such as the respiratory gating technique, breath-holding or tracking, could lead to smaller target volumes and less irradiation of normal tissues. However, the dosimetric gain with the gating plan strongly correlated with tumor mobility in the cranial–caudal direction. Engelsman *et al.* reported that gating would be valueless for tumor motion of less than 1 cm [17], a finding that is in accordance with our previous study [18]. As the amplitude of movement of abdominal LNs is less than 1 cm for the majority of patients, building a ITV based on full 4DCT scans instead of gating is both reasonable and necessary. Furthermore, whether the combination of gating procedures and arc therapy delivery on Elekta accelerators is feasible remains an unanswered question.

In conclusion, VMAT produces highly conformal dose distributions equivalent to conventional IMRT, and is superior to the conformal technique in terms of target coverage and sparing of most OARs. Compared with IMRT, VMAT can achieve higher delivery efficiency and a shorter treatment time, thereby reducing the impact of error introduced by intrafractional variation. However, the superiority of VMAT in delivery efficiency is limited, mainly due to the characteristics of Elekta accelerators. Taking into account plan quality, treatment efficiency and delivery accuracy, VMAT plans generated by Monaco are clinically feasible for treatment of abdominal LN metastasis.

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