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RapidArc combined with the active breathing coordinator provides an effective and accurate approach for the radiotherapy of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a common malignancy that occurs in humans, and only 30–40% of patients are diagnosed at an early stage of the disease [1]. Although treatment options exist for primary HCC, radiotherapy has become an effective strategy for patients with unresectable HCC [1, 2]. Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) has been applied to HCC radiotherapy, and high-dose local radiotherapy was feasible and effective for treating unresectable HCC [4, 5, 6, 7]. IMRT can spare more organs at risk (OARs) with highly conformal and homogeneous dose distribution than 3D-CRT. However, some problems exist with IMRT, such as a long delivery time with more monitor units per fraction, which may affect the accuracy of treatment because of increased intrafractional patient motion and damage to normal tissue [8, 9].

Volumetric modulated arc therapy with the RapidArc (RA, Medical Systems, Palo Alto, CA, USA) and VMAT™ (Elekta Group, Crawley, UK) technique has been used in clinical practice for the treatment of various cancers [10, 11, 12, 13, 14, 15, 16, 17, 18, 19], including HCC [14]. For radiotherapy of HCC, target volume delineation is greatly affected by respiratory motion [20]. A larger margin (internal target volume) than needed is commonly added based on the gross tumor volume (GTV) to assure adequate coverage, which could cause radiation-induced injury of organs at risk (OAR). However, respiratory motion was widely variable in different patients, making it difficult to determine a completely safe margin [13]. For precise positioning of the tumor target volume, an active breathing coordinator (ABC) device has been used in 3D-CRT for the treatment of HCC [20, 21, 22]. The 3D-CRT associated with ABC in HCC radiotherapy spared more of the normal liver tissue and assured the accuracy of the target volume. However, the disadvantage of the relatively long beam-on time of each field in IMRT limits its combination with ABC, and few reports have studied the combination of IMRT and ABC.

Compared to conventional IMRT, RA achieves intensity-modulated radiotherapy with continuous rotation of the gantry combined with the dynamic multiple leaf collimator (MLC) [23]. Volumetric modulated arc therapy achieves better planning target volume (PTV) coverage, and the dose distribution becomes noticeably smoother with fewer monitor units and a shorter treatment time [10, 11, 12, 13, 14, 15, 16, 17, 24]. Because the MLC of static gantry IMRT required carriage movement to cover a large volume from left to right, while the MLC of RapidArc moves back and forth repeatedly during rotation of the gantry, IMRT requires an excessive number of monitor units (MU). Using RA in conjunction with ABC for HCC has not been reported to date.

In this study, 3D-CRT, IMRT, and RA plans using three breathing techniques (free-breathing, (FB), end inspiration hold (EIH), or end expiration hold (EEH)) were designed for patients with HCC. We investigated the feasibility and the dosimetric features of RA associated with ABC for HCC radiotherapy.

Materials and methods

Patients

Twelve randomly selected patients (2 females and 10 males, median age 56 years, range 52–60 years) with pathologically confirmed HCC who were treated at our hospital from January 2010 to January 2011 were included in the study. The cardiopulmonary function of each patient was examined before the study was performed to ensure that they could coordinate with the ABC. The breathing hold time was over 30 s [22, 25]. All patients accepted iodized oil transcatheter arterial chemoembolization (TACE) treatment that was well deposited in the tumor region. The study was approved by the Research Ethics Board of Shandong Cancer Hospital and informed consent was obtained from all patients.

CT simulation and PTV acquisition

Simulations were performed with a Philips Brilliance CT Big Bore (Phillips Medical

Systems, 96 Highland Heights, OH, USA) associated with the Elekta active breathing coordinator™ (ABC) system (Synergy 102™, Elekta, Crawley, UK). Before simulation, breathing training was conducted. The patients were immobilized by vacuum pillow with their hands above their head. The CT scanning region extended from 4 cm of the upper edge of the diaphragm to 4 cm of the lower edge of the right kidney, with 3 mm reconstruction slice thickness. After the CT scans were obtained for FB (CT_{FB}), the EIH CT scans (CT_{EIH}) and EEH CT scans (CT_{EEH}) associated with ABC were performed. All CT scans were obtained in a spiral scan model (pitch = 0.938, table speed = 30 mm/s, reconstruction slice thickness = 3.0 mm) [26, 27]. The CT images were transmitted to the treatment planning system Varian Eclipse V8.6.15 (Varian Medical Systems, Palo Alto, CA, USA) for target volume contouring and plan designing.

GTVs were contoured under the same window width (200 Hu) and level (40 Hu) on CT_{FB}, CT_{EIH}, and CT_{EEH}, and labeled as GTV_{FB}, GTV_{EIH}, and GTV_{EEH}, respectively. PTV_{EIH} and PTV_{EEH} were obtained from GTV_{EIH} and GTV_{EEH}, respectively, plus 8 mm margins isotropically [20]. PTV_{FB} was obtained using 2 cm margins at the craniocaudal direction and 1.5 cm margins in the left–right and anterior–posterior directions (all margins contained the breath motion and setup errors) [28, 29, 30, 31, 32]. The liver, stomach, and duodenum were also delineated. Normal liver was defined as the volume of liver minus the PTV.

Radiotherapy plan design requirements

3D-CRT, IMRT, and RA plans were designed based on CT_{FB}, CT_{EIH}, and CT_{EEH}, respectively. The tumor dose was 50 Gy (2.0 Gy/fraction × 25 fractions) administered at the isocenter with inhomogeneity correction. The requirements for tumor dose coverage were as follows: the PTV had to be covered by the prescription dose, and inhomogeneity had to be less than 10% [18]. The dose constraints for OAR were as follows: the mean dose of normal liver was limited to 23 Gy, and the dose–volume histogram (DVH) of normal liver was within the tolerance area (i.e., $V_5 < 86\%$, $V_{10} < 68\%$, $V_{20} < 49\%$, $V_{30} < 28\%$, and $V_{40} < 20\%$) [34]; for the stomach and duodenum, the maximum dose was limited to 45 Gy, and the volume receiving > 25 Gy was limited to < 5 cm^3 [35].

Radiotherapy plans

1. 3D-CRT plans: 4–7 coplanar radiation fields were used, and the weight and gantry angle as well as the shape, size, and angle of the multiple leaf collimator (MLC) of every field were adjusted to meet the dose requirements. The dose rate was set at 300 MU/min.
2. IMRT plans: 5 coplanar radiation fields were designed using the step-static approach, and the gantry angles were not divided equally. The dose rate was set at 400 MU/min.
3. RA plans: Three 135 ° arc coplanar fields were applied and optimized simultaneously. Two arcs overlapped in the liver region. The maximum dose rate was set at 600 MU/min.

The planning objectives were as follows: 98% of the volume of PTV reached 95% of the prescription dose, with 10% of the volume of PTV not exceeding 110% of the prescription dose. The 100% prescription dose of all plans was normalized to the PTV mean dose. All plans were optimized for Varian Trilogy equipped with MLC with a leaf width of 5 mm at the isocenter in the inner 20 cm, and 10 mm for the outer 2 × 10 cm for a 15 MV photon beam. Dose distributions were computed with the Analytical Anisotropic Algorithm (AAA) implemented in the Eclipse 8.6.15 treatment planning system with a maximum calculation grid resolution of 2.5 mm [16].

Planning evaluation

For PTV, the $D_{1\%}$ and $D_{99\%}$ (doses to 1% and 99% volume of the PTV, respectively) were the maximum and minimum dose, respectively. The conformality index (CI) was calculated as the Van't Riet definition:

$$CI = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}} \quad (1)$$

where TV_{RI} is the target volume covered by the reference isodose, TV is the target volume, and V_{RI} is the volume of the reference isodose. The homogeneity index (HI) was defined as

$$HI = 1 - \frac{D_{2\%} - D_{98\%}}{prescription\ dose} \quad (2)$$

The CI and HI ranges from 0 to an ideal value of 1 [33]. The mean irradiated dose of normal liver (D_{mean}), V_5, V_{10}, V_{20}, V_{30}, and V_{40}, where V_x represents the percentage of the volume of x Gy in the volume of normal liver [34], and the maximum doses (D_{max}) of the stomach and duodenum and the irradiated dose received by 5_{cm^3} of volume (D_{5cm^3}) were also recorded and compared [35].

Statistics analysis

SPSS 16.0 (IBM, Chicago, IL, USA) was used for the statistical analyses. The Friedman test was used to compare three groups of data. The paired *Wilcoxon* test was used to compare the pairwise data. A $p < 0.05$ represented statistical significance.

Results

Target volume comparison

All patients completed the CT simulation associated with ABC. The diaphragmatic mobility measured by CT_{EIH} and CT_{EEH} images averaged 1.3 cm (0.71–1.90 cm). No significant difference occurred in the volume of liver, normal liver, and GTVs between EIH, EEH, and FB ($p > 0.05$). PTV_{FB} was significantly larger than the PTV_{EIH} and PTV_{EEH} ($p < 0.05$). The mean value of PTV_{FB}/PTV_{EIH} and PTV_{FB}/PTV_{EEH} were 1.94 and 1.835, respectively, while no significant difference between PTV_{EIH} and PTV_{EEH} was observed ($p > 0.05$) (**Tab. 1**).

Target coverage and dose homogeneity

All plans met the requirements for tumor dose coverage and OAR dose limitation (**Fig. 1**). The CI and HI of RA were significantly better than IMRT and

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RapidArc combined with the active breathing coordinator provides an effective and accurate approach for the radiotherapy of hepatocellular carcinoma

Abstract

Purpose. The goal of this research was to investigate the feasibility of volumetric modulated arc therapy, RapidArc (RA), in association with the active breathing coordinator (ABC) for the treatment of hepatocellular carcinoma (HCC) with radiotherapy.

Patients and materials. A total of 12 patients with HCC, after receiving transcatheter arterial chemoembolization (TACE) treatment, underwent three-dimensional computer tomography (3D-CT) scanning associated with ABC using end inspiration hold (EIH), end expiration hold (EEH), and free breathing (FB) techniques. The three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and RA plans (three 135° arcs) were designed on different CT images, respectively. The liver volume, gross tumor volume (GTV), and planning target volume (PTV) of the three breath status and the dosimetric differences of the different plans were compared.

Results. There were no significant differences in the volumes of live and GTV between the three breathing techniques ($p > 0.05$); the PTV in FB was greater than in the EEH and EIH ($p < 0.05$). The overall conformality index (CI) and homogeneity index (HI) for RA (CI 0.92, HI 0.90) were better than IMRT (CI 0.90, HI 0.89) and 3D-CRT (CI 0.70, HI 0.84) for the three breathing techniques ($p < 0.05$). The RA and IMRT significantly reduced the mean dose, V_{20}, V_{30}, and V_{40} of normal liver compared to 3D-CRT, while the V_5 and V_{10} in RA were higher than in IMRT. The mean values in mean dose, V_{10}, V_{20}, V_{30}, and V_{40} of the normal liver were reduced from 13.12 Gy, 46%, 24%, 13%, and 8% in RA_{FB} to 10.23 Gy, 35%, 16%, 8%, and 5% in RA_{EEH} and 9.23 Gy, 32%, 16%, 8%, and 5% in RA_{EIH}, respectively. In addition, the treatment time of RA was equal to 3D-CRT, which was significantly shorter than IMRT.

Conclusion. RA in conjunction with ABC for the treatment of HCC with radiotherapy can achieve better dose delivery and ensure the accuracy of the target volume, which spares more organs at risk, uses fewer monitor units, and shortens treatment time.

Keywords

Hepatocellular carcinoma · Radiotherapy · Active breathing coordinator · Volumetric modulated arc therapy · Conformal radiotherapy

RapidArc in Verbindung mit aktiver Atemkoordination ist eine wirksame und genaue Vorgehensweise bei der Strahlentherapie des hepatozellulären Karzinoms

Zusammenfassung

Ziel. Prüfung der Möglichkeit der volumetrisch modulierten Bogentherapie, RapidArc (RA), in Verbindung mit einer aktiven Atemkoordination („activ breathing coordinator", ABC) bei der Behandlung von hepatozellulären Karzinomen („hepatocellular carcinoma", HCC) mit Strahlentherapie.

Patienten und Material. Insgesamt 12 Patienten mit HCC unterzogen sich nach einer transkatheter-arteriellen Chemoembolisation („transcatheter arterial chemoembolization", TACE)-Behandlung einer dreidimensionalen Computertomographie (3D-CT), verbunden mit einer aktiven Atemkoordination (ABC), die Endinspirationsfluss („end inspiration hold", EIH), Endexpirationsfluss („end expiration hold", EEH) und freie Atmung („free breathing", FB) einbezog. Die 3D-konforme Strahlentherapie (3D-CRT), die intensitätsmodulierte Strahlentherapie (IMRT) und die RA-Pläne (drei 135°-Bögen) wurden jeweils auf verschiedenen CT-Bildern entworfen. Das Lebervolumen, das Gesamttumorvolumen („gross tumor volume", GTV) und das Planzielvolumen („plan target volume", PTV) wurden unter Anwendung von 3 Atemtechniken verglichen, ebenso die dosimetrischen Unterschiede der verschiedenen Pläne.

Ergebnisse. Es gab keine signifikanten Unterschiede bezüglich des Lebervolumens und des GTV bei den 3 Atemtechniken ($p > 0{,}05$); jedoch war das PTV in FB größer als im EEH und im EIH ($p < 0{,}05$). Der globale konformale Index („conformal index", CI) und Homogenitätsindex („homogeneity index", HI) für RA (CI 0,92; HI 0,90) waren für die 3 Atemtechniken ($p < 0{,}05$) besser als IMRT (CI 0,90; HI 0,89) und 3D-CRT (CI 0,70; HI 0,84). Die RA- und IMRT-Pläne verringerten im Vergleich zu 3D-CRT erheblich die mittlere Dosis, V_{20}, V_{30} und V_{40} der normalen Leber, während V_5 und V_{10} in RA höher waren als bei IMRT. Beim Vergleich der RA-Pläne für die verschiedenen Atemtechniken verringerten sich die mittlere Dosis, V_{10}, V_{20}, V_{30} und V_{40} der normalen Leber von 13,12 Gy, 46%, 24%, 13% und 8% bei RA_{FB} auf 10,23 Gy, 35%, 16%, 8% und 5% bei RA_{EEH} und auf 9,23 Gy, 32%, 16%, 8% und 5% bei RA_{EIH}. Darüber hinaus war die Behandlungzeit von RA identisch mit der von 3D-CRT und damit erheblich kürzer als IMRT.

Zusammenfassung. RA in Verbindung mit ABC für die Behandlung von HCC mit Strahlentherapie kann eine bessere Strahlungsdosis erzielen und die Genauigkeit des Zielvolumens sicherstellen, was gefährdete Organe („organs at risk", OARs) besser schont. Zudem werden weniger Anzeigegeräte benötigt, und die Behandlungzeit wird kürzer.

Schlüsselwörter

Hepatozelluläres Karzinom · Strahlentherapie · Aktive Atmenkoordination · Volumetrisch modulierte Bogentherapie · Konformale Strahlentherapie

3D-CRT ($p < 0.05$; **Tab. 2**). The maximum dose of PTV in 3D-CRT was greater than RA and IMRT ($p < 0.05$). Moreover, there was no significant difference in the minimum dose of target volume among the three plans ($p > 0.05$). No significant difference in CI, HI, and the minimum dose and maximum dose of PTV was observed among RA plans in FB, EIH, and EEH ($p > 0.05$; **Tab. 2 and Fig. 2**).

Organs at risk

The D_{mean}, V_{10}, V_{20}, V_{30}, and V_{40} of normal liver in 3D-CRT was greater than RA and IMRT ($p < 0.05$), while the V_5 and V_{10} in RA were higher than in IMRT. In contrast, no statistically significant differ-

Tab. 1 The volume difference of liver, normal liver, GTV, and PTV between EIH, EEH, and FB techniques

	EIH	EEH	FB		
	$\bar{x} \pm SD$ (cm^3)			χ^2	p
Liver	1,336 ± 358	1,335 ± 396	1,397 ± 411	4.72	0.09
GTV	16.81 ± 15.2	17.04 ± 15.1	17.55 ± 14.7	0.00	1.00
PTV	83.1 ± 43.8	89.5.4 ± 44.7	160.8 ± 78.7	11.17	0.004
Normal liver	1,271 ± 352	1,264 ± 391	1,295 ± 401	0.17	0.92

EIH end inspiration hold, EEH end expiration hold, FB free breathing, GTV gross tumor volume, PTV planning tumor volume, SD standard deviation.

Tab. 2 The target coverage and dose homogeneity difference between 3D-CRT, IMRT, and RA; as well as the differences between RA plans in FB, EEH, and EIH

Differences between 3D-CRT, IMRT, and RA					Differences between RA plans in FB, EEH, and EIH			
		$\bar{x} \pm SD$	χ^2	p		$\bar{x} \pm SD$	χ^2	p
CI	3D-CRT	0.77 ± 0.043	53.39	0.00	EIH	0.92 ± 0.03	1.17	0.56
	IMRT	0.90 ± 0.037			EEH	0.93 ± 0.02		
	RA	0.92 ± 0.049			FB	0.92 ± 0.05		
HI	3D-CRT	0.84 ± 0.021	51.06	0.00	EIH	0.90 ± 0.03	1.50	0.47
	IMRT	0.89 ± 0.02			EEH	0.89 ± 0.02		
	RA	0.90 ± 0.024			FB	0.89 ± 0.03		
$D_{1\%}$	3D-CRT	57.21 ± 1.25	19.50	0.00	EIH	55.71 ± 0.69	4.500	0.11
	IMRT	55.69 ± 1.05			EEH	56.21 ± 1.22		
	RA	56.12 ± 1.09			FB	56.52 ± 1.12		
$D_{99\%}$	3D-CRT	44.95 ± 1.83	3.37	0.19	EIH	45.08 ± 0.96	4.500	0.11
	IMRT	45.06 ± 1.56			EEH	44.42 ± 1.03		
	RA	44.65 ± 1.31			FB	43.78 ± 1.88		

CI conformality index, HI homogeneity index, 3D-CRT three-dimensional conformal radiotherapy, IMRT intensity-modulated radiotherapy, RA RapidArc; FB free breathing, EEH end expiration hold, EIH end inspiration hold, $D_{x\%}$ dose to x% volume, SD standard deviation.

Tab. 3 The dose–volume difference of organs at risk between 3D-CRT, IMRT, and RA

		$\bar{x} \pm SD$	χ^2	*p*			$\bar{x} \pm SD$ (Gy)	χ^2	*p*
Normal Liver V_5	CRT	57 ± 21.0	4.50	0.11	Normal liver D_{mean}	CRT	11.66 ± 3.43	6.89	0.03
	IMRT	53 ± 19.0				IMRT	10.81 ± 3.91		
	RA	54 ± 9.0				RA	11.14 ± 4.36		
Normal liver V_{10}	CRT	37 ± 13.0	5.39	0.07	Stomach D_{max}	CRT	22.09 ± 20.97	2.72	0.26
	IMRT	34 ± 13.0				IMRT	23.19 ± 21.29		
	RA	37 ± 14.0				RA	22.79 ± 22.25		
Normal liver V_{20}	CRT	24 ± 9.0	12.39	0.00	Stomach D_{5cm^3}	CRT	20.17 ± 13.74	0.17	0.92
	IMRT	20 ± 8.6				IMRT	20.03 ± 13.78		
	RA	19 ± 8.1				RA	17.52 ± 12.88		
Normal liver V_{30}	CRT	13 ± 5.5	18.06	0.00	Duodenum D_{max}	CRT	26.39 ± 16.34	0.17	0.92
	IMRT	10 ± 4				IMRT	26.58 ± 15.80		
	RA	10 ± 5				RAc	25.08 ± 15.97		
Normal liver V_{40}	CRT	8 ± 4	10.50	0.01	Duodenum D_{5cm^3}	CRT	12.37 ± 13.70	10.56	0.46
	IMRT	5 ± 3				IMRT	12.79 ± 14.27		
	RA	6 ± 4				RA	13.26 ± 15.36		

CRT conformal radiotherapy, IMRT intensity-modulated radiotherapy, RA RapidArc, V_x represents the percentage of the volume of x Gy in the volume of normal liver, $D_{x\%}$ dose to x% volume, SD standard deviation.

ence was found in V_5, V_{10} of normal liver, D_{max}, and D_{5cm^3} of the stomach and duodenum between 3D-CRT, IMRT, and RA ($p > 0.05$) (Tab. 3).

The D_{mean}, V_5, V_{10}, V_{20}, V_{30}, and V_{40} of RA in FB were larger than those in EEH and EIH ($p < 0.05$), but there was no statistically significance difference in V_5 and V_{40} among the three respiration techniques. No significant difference was found in all of these indices between RA in EEH and EIH, and D_{5cm^3} of stomach and the D_{max} of duodenum did not differ significantly among the three respiration techniques ($p > 0.05$). The stomach D_{max} of RA plans in FB was significantly larger than EEH and EIH ($p < 0.05$), while the duodenum D_{5cm^3} of the RA plans in EEH was significantly smaller than FB and EIH ($p < 0.05$) (Tab. 4, Fig. 3).

Monitor units and delivery time

The monitor unit in the IMRT plans (626.33 ± 113.97 MU) was significantly greater than RA (550.28 ± 122.56 MU) and 3D-CRT (254.06 ± 18.59 MU) ($p < 0.05$). The treatment time (from first filed beam-on to the last filed beam-off) in RA (130 ± 10 s) was similar to 3D-CRT (135 ± 10 s), but was significantly less than IMRT (540 ± 45 s) ($p < 0.05$).

Discussion

Volumetric modulated arc radiotherapy has been investigated for the treatment of various cancers [11, 12, 13, 14, 15, 16, 17, 18, 19], and RA has been shown to achieve better dose coverage than traditional IMRT using a markedly shorter treatment time. We compared RA with IMRT plans and showed that RA achieved conformal degrees with shorter treatment times and fewer monitor units [14]. Here, RA associated with ABC in HCC radiotherapy achieved better target coverage and spared more OARs using shorter treatment times.

The main advantage of incorporating ABC with RA in HCC radiotherapy is to reduce the negative effects on OARs. We compared dose–volume parameters for normal liver, stomach, and duodenum and found that normal liver tissue had the highest risk of damage during ra-

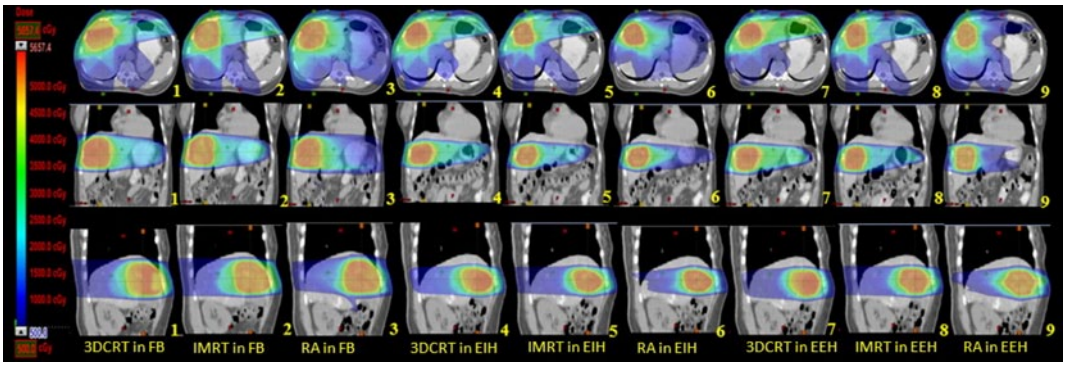

Fig. 1 ◀ The dose distribution features of the different plans (100 cGy = 1 Gy). All of the plans met the clinical requirements, and PTV_{EEH} and PTV_{EIH} were smaller than PTV_{FB}. The RA_{EEH} and RA_{EIH} plans significantly reduce the normal liver radiation dose compared to RA_{FB} ($p < 0.05$)

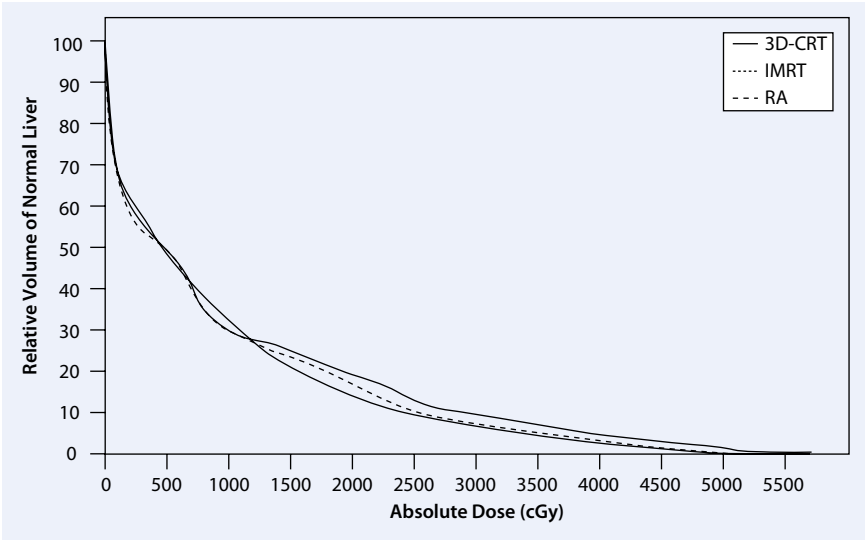

Fig. 2 ▲ The dose–volume relationship of normal liver between three-dimensional conformal radiotherapy (*3D-CRT*), intensity-modulated radiotherapy (*IMRT*), and RapidArc (*RA*) (100 cGy = 1 Gy). RA and IMRT plans significantly reduce the V_{30} of normal liver ($p < 0.05$)

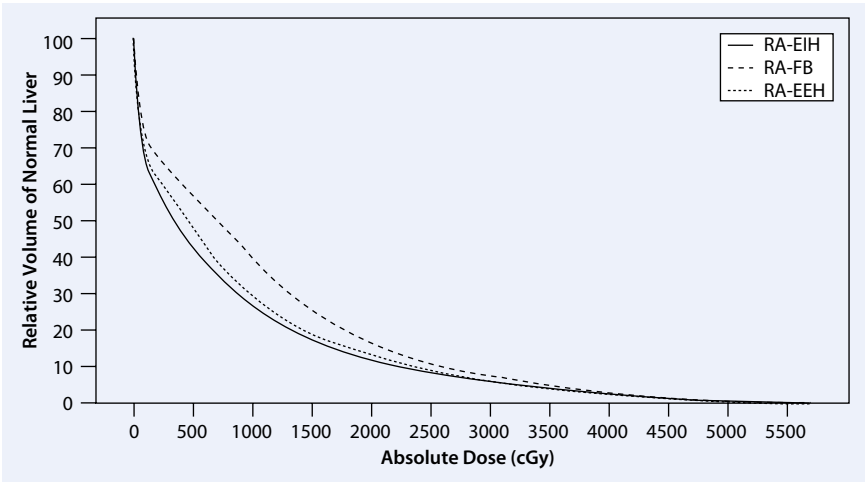

Fig. 3 ▲ The dose–volume relationship of normal liver among RapidArc(*RA*) plans in free breathing (*FB*), end expiration hold (*EEH*), and end inspiration hold (*EIH*). The RA plans in EEH and EIH significantly reduce the normal liver radiation dose ($p < 0.05$). 100 cGy = 1 Gy

diotherapy [28]. Radiotherapy associated with ABC reduced the volume of the PTV with an accurate determination of the position and target volume. RA and IMRT significantly reduced the D_{mean}, V_{20}, V_{30}, and V_{40} of normal liver compared to 3D-CRT, and RA plans in EIH and EEH significantly reduced the D_{mean}, V_5, V_{10}, V_{20}, V_{30}, and V_{40} compared to RA plans in FB. RA associated with ABC can reduce the D_{mean} and V_{30} of normal liver with perfect PTV dose coverage, which may lower the incidence of RT-induced liver disease (RILD) [36]. The stomach and duodenum are also at risk for damage during HCC radiotherapy. No significant difference in the D_{max} and D_{5cm^3} of these organs between 3D-CRT, IMRT, and RA was observed, possibly due to the smaller tumor volume.

When ABC is implemented into the RA process, the size of the arcs at different rotations is critical. Most RA plans and treatments use single or two 358° whole rotation arcs or rotation arcs over 180°. The whole arc was used in designing RA plans, and the segmenting treatment was considered at the beginning of our study. However, during treatment, if the beam were suddenly beam-offed, the gantry of the linear accelerator will move forward due to inertia, which may cause mechanical failure. Moreover, if the treatment was interrupted during the entire arc, the gantry would return to the initial position and run empty to the location of the interruption. The gantry would then re-administer the beams, so the total treatment time would be prolonged. Three 135° small arcs were used in this study, and the linear accelerator used had an angular velocity of 4.8°/s. The treatment time for each arc was approximately 28 s. Breaks for patient rest

Tab. 4 The dose–volume difference of organs at risk among RA plans in FB, EEH, and EIH

		$\bar{x} \pm SD$	χ^2	p			$\bar{x} \pm SD$ (Gy)	χ^2	p
Normal Liver V_5	EIH	48 ± 16.0	5.17	0.76	Normal liver D_{mean}	EIH	9.23 ± 3.35	8.67	0.01
	EEH	53 ± 17.0				EEH	10.23 ± 3.58		
	FB	62 ± 22.0				FB	13.12 ± 5.42		
Normal liver V_{10}	EIH	32 ± 12.0	6.50	0.039	Stomach D_{max}	EIH	24.18 ± 13.32	4.67	0.097
	EEH	35 ± 12.0				EEH	24.51 ± 15.25		
	FB	46 ± 18.0				FB	28.84 ± 18.38		
Normal liver V_{20}	EIH	16 ± 6.0	8.00	0.018	Stomach D_{5cm^3}	EIH	16.04 ± 12.10	2.167	0.338
	EEH	16 ± 6.0				EEH	17.68 ± 13.72		
	FB	24 ± 10.0				FB	18.84 ± 13.76		
Normal liver V_{30}	EIH	8 ± 3.0	12.50	0.02	Duodenum D_{max}	EIH	15.48 ± 21.63	4.167	0.125
	EEH	8 ± 3.0				EEH	22.29 ± 21.14		
	FB	13 ± 6.0				FB	30.61 ± 23.13		
Normal liver V_{40}	EIH	5 ± 3.0	4.67	0.10	Duodenum D_{5cm^3}	EIH	11.67 ± 13.25	6.50	0.039
	EEH	5 ± 3.0				EEH	8.78 ± 13.31		
	FB	8 ± 5.0				FB	19.35 ± 18.38		

FB free breathing, **EEH** end expiration hold, **EIH** end inspiration hold, V_x represents the percentage of the volume of x Gy in the volume of normal liver, $D_{x\%}$ dose to x% volume, **SD** standard deviation.

and gantry preparation take approximately 30 s, so the treatment could be completed within 115 s, which is equivalent to the time for 3D-CRT and much shorter than IMRT. The breath holding time limited the size of each arc for RapidArc in combination with ABC. It was previously demonstrated that "there was no measurable diaphragm or hepatic microcoil movement during 30 s ABC breath holds in any of the patients treated with ABC" [20]. Here, the breath holding time of patients reached 30 s after training. We believe the breath training is very important for the progress of radiotherapy using ABC, and is a simple and effective way to assure reproducibility and stability of respiration motion. However, patients should not hold their breath for too long, because it could fatigue respiratory muscles, which could affect the accuracy of dose distribution.

The breath function and cooperation of each patient were important when the breathing techniques were selected for radiotherapy associated ABC. We compared FB, EIH, and EEH hold without using the end of deep inspiration hold (EDIH) or end of deep expiration hold (EDEH). First, greater mobility was investigated in the EDIH and EDEH, which may affect the location relationship between the liver and surrounding organs, thereby affecting the dose–volume relationship of OARs [37]. Second, the deep inspiration and expiration required good respiratory functions and the coordination ability of the patients. The respiratory ranges of each patient in EIH or EEH had to spontaneously reach the trigger threshold and exhibit good reproducibility. Here, the difference in the D_{5cm^3} of the duodenum may be related to the target volume and duodenum position becoming distant in EEH. For selection of EIH and EEH, the respiratory functions, coordination ability, and other specific conditions should be considered.

Our study provides guidance for radiotherapy using RA for tumors that are affected by respiratory motion. Unfortunately, we did not use an image-guided system, and some reports suggest that image-guided radiotherapy (IGRT) achieved by cone beam computer tomography and ultrasound can spare more OARs and ensure an accurate target volume [38, 39, 40, 41]. Applying the IGRT system could evaluate the irradiation dose of the PTV, which may be efficacious against cancers without increasing toxicity [40, 41, 42]. Sometimes, the IGRT system requires implanted fiducials in the tumor [40], and lipiodol is a direct surrogate for CBCT image guidance for radiotherapy of HCC after TACE [43]. Image-guided system associated with ABC can increase the overall precision of target volume [43, 44, 45]. Image-guided RA in combination with ABC may become an effective and accurate way to administer HCC radiotherapy.

Conclusion

The use of RA with three arcs of 135° associated with ABC is a feasible method for HCC radiotherapy and provides equal or better target coverage than IMRT. It also provides better protection of normal tissue and improves treatment efficiency, and may become an effective method for administering HCC radiotherapy with perfect dose delivery. However, the advantage of this strategy should be explored in additional studies.

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References

1. Wörns MA, Galle PR (2010) Future perspectives in hepatocellular carcinoma. Dig Liver Dis 42(Suppl 3):302–309
2. Whang-Peng J, Cheng AL, Hsu C et al (2010) Clinical development and future direction for the treatment of hepatocellular carcinoma. J Exp Clin Med 2(3):93–103
3. Seong J, Park HC, Han KH et al (2003) Clinical results and prognostic factors in radiotherapy for unresectable hepatocellular carcinoma a retrospective study of 158 patients. Int J Radiat Oncol Biol Phys 55(2):329–336
4. Merle P, Mornex F, Trepo C et al (2009) Innovative therapy for hepatocelluar carcinoma: three-dimensional high-dose photon radiotherapy. Cancer Lett 286:129–133
5. Tokuuye K, Sumi M, Kagami Y et al (2000) Radiotherapy for hepatocellular carcinoma. Strahlenther Onkol 176:406–410
6. Hata M, Tokuuye K, Sugahara S, et al (2007) Proton irradiation in a single fraction for hepatocellular carcinoma patients with uncontrollable ascites: technical considerations and results. Strahlenther Onkol 183:411–416

7. Sugahara S, Nakayama H, Fukuda K et al (2009) Proton-beam therapy for hepatocellular carcinoma associated with portal vein tTumor thrombosis. Strahlenther Onkol 185:782–788
8. Gierga D, Chen G, Kung J et al (2004) Quantification of respiration-induced abdominal tumor motion and its impact on IMRT dose distributions. Int J Radiat Oncol Biol Phys; 58 (5):1584–1595
9. Wang, JZ, Li XA, D'Souza WD et al (2003) Impact of prolonged fraction delivery times on tumor control probability: a note of caution for IMRT. Int J Radiat Oncol Biol Phys 57(2):543–552
10. Cozzi L, Dinshawc KA, Shrivastavac SK (2008) A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy. Radiother Oncol 89:180–191
11. Eppinga W, Lagerwaard F, Verbakel W et al (2010) Volumetric modulated arc therapy for advanced pancreatic cancer. Strahlenther Onkol 186:382–387
12. Jacob V, Bayer W, Astner ST et al (2010) A planning comparison of dynamic IMRT for different collimator leaf thicknesses with helical tomotherapy and RapidArc for prostate and head and neck tumors. Strahlenther Onkol 186:502–510
13. Bignardi M, Cozzi L, Fogliata A et al (2009) Critical appraisal of volumetric modulated arc therapy in stereotactic body radiation therapy for metastases to abdominal lymph nodes. Int J Radiat Oncol Biol Phys 75(5):1570–1577
14. Yin Y, Ma C, Gao M et al (2010) Dosimetric comparison of rapidarc with fixed gantry intensity-modulated radiotherapy treatment for multiple liver metastases radiotherapy. Med Dosim 35:448–454
15. Popescu CC, Olivotto IA, Beckham WA et al (2010) Volumetric modulated arc therapy improves dosimetry and reduces treatment time compared to conventional Intensity-Modulated radiotherapy for locoregional radiotherapy of left-sided breast cancer and internal mammary nodes. Int J Radiat Oncol Biol Phys 76(1):287–295
16. Scorsetti M, Bignardi M, Alongi F et al (2011) Stereotactic body radiation therapy for abdominal targets using volumetric intensity modulated arc therapy with RapidArc: feasibility and clinical preliminary results. Acta Oncol 50(4):528–538
17. Shaffer R, Nichol AM, Vollans E et al (2010) A comparison of volumetric modulated arc therapy and conventional Intensity – modulated radiotherapy for frontal and temporal high-Grade gliomas. Int J Radiat Oncol Biol Phys 76(4):1177–1184
18. Wolff D, Stieler F, Hermann B et al (2010) Clinical implementation of volumetric intensity-modulated arc therapy (VMAT) with ERGO++. Strahlenther Onkol 186:280–288
19. Stieler F, Wolff D, Bauer L et al (2011) Reirradiation of spinal column metastases-comparison of several treatment techniques and dosimetric validation for the use of VMAT. Strahlenther Onkol 187:406–415
20. Dawson LA, Brock KK, Kazanjian S et al (2001) The reproducibility of organ position using active breathing coordinator (ABC) during liver radiotherapy. Int J Radiat Oncol Biol Phys 51(5):1410–142
21. Eccles C, Brock K, Bissonnette J et al (2006) Reproducibility of liver position using active breathing coordinator for liver cancer radiotherapy. Int J Radiat Oncol Biol Phys 64(3):751–759
22. Zhao JD, Xu ZY, Zhu J et al (2008) Application of active breathing coordinator in 3-dimensional conformal radiation therapy for hepatocellular carcinoma: the feasibility and benefit. Radiother Oncol 87:439–444
23. Palma DA, Verbakel WFAR, Otto K et al (2010) New developments in arc radiation therapy: a review. Cancer Treat Rev 36:393–399
24. Bortfeld T (2010) The number of beams in IMRT—theoretical investigations and implications for single-arc IMRT. Phys Med Biol 55:83–97
25. Dawson L, Eccles C, Bissonnette J et al (2005) Accuracy of daily image guidance for hypofractionated liver radiotherapy with active breathing coordinator. Int J Radiat Oncol Biol Phys 62(4):1247–1252
26. Skrzyński W, Zielińska-Dąbrowska S, Wachowicz M et al (2010) Computed tomography as a source of electron density information for radiation treatment planning-CT. Strahlenther Onkol 186:327–333
27. Zurl B, Stranzl H, Winkler P et al (2010) Quantitative assessment of irradiated lung volume and lung mass in breast cancer patients treated with tangential fields in combination with deep inspiration breath hold (DIBH). Strahlenther Onkol 186:157–162
28. Guckenberger M, Kavanagh A, Webb S et al (2011) A novel respiratory motion compensation strategy combining gated beam delivery and mean target position concept – a compromise between small safety margins and long duty cycles. Radiother Oncol 98:317–322
29. Guckenberger M, Richter A, Wilbert J et al (2010) Adaptive radiotherapy for locally advanced non-small cell lung cancer does not underdose the microscopic disease and has the potential to increase tumor control. Int J Radiat Oncol Biol Phys, doi:10.1016/j.ijrobp.2011.01.067
30. Guckenerger M, Wilbert J, Richter A et al (2011) Potential of adaptive radiotherapy to escalate the radiation dose in combined radiochemotherapy for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 79:901–908
31. Guckenberger M, Sweeney R Wilbert J et al (2008) Image-guided radiotherapy for liver cancer using respiratory-correlated computed tomography and cone-beam computed tomography. Int J Radiat Oncol Biol Phys 71:297–304
32. Seong J, Park HC, Han KH et al (2003) Clinical results and prognostic factors in radiotherapy for unresectable hepatocellular carcinoma a retrospective study of 158 Patients. Int J Radiat Oncol Biol Phys 55(2):329–336
33. Cilla S, Macchia G, Digesù C et al (2010) 3D-conformal versus intensity-modulated postoperative radiotherapy of vaginal vault: a dosimetric comparison. Med. Dosim 35(2):135–142
34. Ren ZG, Zhao JD, Gu K et al (2011) Three-dimensional conformal radiation therapy and intensity-modulated radiation therapy combined with transcatheter arterial chemoembolization for locally advanced hepatocellular carcinoma: an irradiation dose escalation study. Int J Radiat Oncol Biol Phys 79(2):496–502
35. Kavanagh BD, Pan CC, Dawson LA et al (2010) Radiation dose–volume effects in the stomach and small bowel. Int J Radiat Oncol Biol Phys 76(3):101–107
36. Pan CC, Kavanagh BD, Dawson LA et al (2010) Radiation-associated liver injury. Int J Radiation Oncology Biol Phys 76 (3 Suppl):S94–S100
37. Stromberg JS, Sharpe MB, Kim LH et al (2000) Active breathing coordinator (ABC) for Hodgkin's disease reduction in normal tissue irradiation with deep inspiration and implications for treatment. Int J Radiat Oncol Biol Phys 48(3):797–806
38. Boda-Heggemann J, Lohr F, Wenz F et al (2011) kV cone-beam CT-based IGRT. Strahlenther Onkol 187:284–291
39. Boda-Heggemann J, Fleckenstein J, Lohr F et al (2011) Multiple breath-hold CBCT for online image guided radiotherapy of lung tumors: simulation with a dynamic phantom and first patient data. Radiother Oncol 98:309–316
40. Graf R, Boehmer D, Budach V et al (2010) Residual translational and rotational errors after kv x-ray image-guided correction of prostate location using implanted fiducials. Strahlenther Onkol 186:544–550
41. Guckenberger M, Ok S, Polat B et al (2010) Toxicity after intensity-modulated, image-guided radiotherapy for prostate cancer. Strahlenther Onkol 186:535–543
42. Boda-H Guckenberger M, Goebel J, Wilbert J et al (2009) Clinical outcome of dose-escalated image-guided radiotherapy for spinal metastases. Int J Radiat Oncol Biol Phys 75:828–835
43. Yue J, Sun X, Cai J et al (2010) Lipiodol: a potential direct surrogate for cone-beam computed tomography image guidance in radiotherapy of liver tumor. Int J Radiat Oncol Biol Phys 82:834–841
44. Boda-Heggemann J, Walter C, Mai S et al (2006) Frameless stereotactic radiosurgery of a solitary liver metastasis using active breathing control and stereotactic ultrasound. Strahlenther Onkol 182:216–221
45. Mack A, Mack G, Weltz D et al (2003) Quality assurance in stereotactic space. Determination of the accuracy of aim and dose in single dose radiosurgery. Strahlenther Onkol 179:760–766