·FAST REPORT·

Internal Target Volume Definition Using Four-dimensional CT and Dosimetric Evaluation for Hepatocellular Carcinoma

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[ABSTRACT] **BACKGROUND & OBJECTIVE:** Accurate definition of target volume is difficult in three-dimensional conformal radiotherapy (3D CRT) for liver tumors because of the wide moving extent of tumors with respiration. This study was to define individualized internal target volume (ITV) using four-dimensional computed tomography (4D-CT), and compare planning target volumes (PTVs) and dose distribution of 3D planning with 4D planning for hepatocellular carcinoma (HCC). **METHODS:** Seven primary HCC patients received 4D-CT scanning. Gross tumor volumes (GTVs) and clinical target volumes (CTVs) were contoured on all 10 respiratory phases of CT images. The 3D and 4D treatment plans were made for each patient using different PTVs, namely, PTV-3D derived from a single CTV plus conventional margins; PTV-4D derived from ITV-4D which encompassing all 10 CTVs plus setup margins (SM). The two plans were designed at the 20% respiratory phase CT images using 3D treatment planning system and compared with respect to PTVs, dose distribution to normal tissues, normal tissue complication probability. The prescription dose and design of irradiating fields were identical for both plans. **RESULTS:** The average PTV was (417.6±197.7) cm^3 in 3D plan and (331.9±183.1) cm^3 in 4D plan, decreased by 20.50% (12.60%-34.40%). PTV coverage and dose uniformity were similar in the 2 plans. 4D plans spared more normal liver, kidney, stomach, and small intestine than 3D plans, especially for the liver. The V30 and V40 of the liver were lower in 4D plans than in 3D plans (33.59% *vs.* 38.77%, 22.62% *vs.* 27.32%); the mean dose to normal liver was decreased from 24.13 Gy to 21.5 Gy; liver complication probability was decreased from 21.57% to 15.86%. Without increasing the normal tissue complication probability, the prescription dose was higher in 4D plans than in 3D plans [(54.86±2.79) Gy *vs.* (50.57±1.51) Gy], increased by 9.72% (4%-16%). **CONCLUSIONS:** The 3D plans have pitfalls of geometric miss or over coverage of target volume. The 4D plans can accurately definite target volume to spare more normal tissues and make dose escalation as compared with 3D CRT.

KEYWORDS: Liver neoplasm/radiotherapy; Three-dimensional treatment planning; Four-dimensional computed tomography (4D-CT); Dosimetry

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and is the second leading cause of cancer in China with a mortality of more than 300,000 cases yearly[1]. With the progression of radiotherapy equipments, computer technology, and the research of radiation biology, especially for the introduction of three-dimensional conformal radiotherapy (3DCRT), the role of radiotherapy for patients with HCC has been reconsidered. Accurate definition of the target volume is difficult in 3DCRT because of the wide extent of motion of the liver tumors with respiration [2,3]. To ensure sufficient dose coverage of target volume throughout the treatment course, margins including internal margin (IM) and setup margin (SM) should be added to clinical target volumes (CTV) to form planning target volumes (PTV). Geometric margins to account for respiratory motion are usually derived from fluoroscopy, clinical experience, or using values reported in the literatures. Such margins are neither accurate nor patient-specific, which have possibility of geometric miss or over coverage of the target volume.

Four-dimensional (4D) radiotherapy is the explicit inclusion of the temporal changes in anatomy during the imaging, planning, and delivery of radiotherapy. 4DCT scans can reliably capture intrafractional tumor mobility for radiotherapy planning and generate accurate internal target volumes (ITV), which cover the movement range of CTV [4,5]. This study was designed to make accurate definition of individualized ITV using 4DCT, compare the target volumes and the dose distribution of 3D planning with 4D planning, and evaluate the clinical significance of 4DCT imaging for HCC.

Materials and Methods

Patient selection and clinical characteristics

Patients were selected according to the following eligibility criteria: (1) the diagnosis of HCC patients, who were either surgically unresectable or refusal to surgery, was based on histological features or on clinical findings; (2) aged from 20 to 70 years; (3) A or B Child-Paugh degree, disease confined to one lobe of the liver, absence of uncontrollable ascites, jaundice, or extrahepatic metastasis; (4) indocyanine green (ICG) retention rate <10% at 15 minutes; (5) Karnofsky performance scale≥ 70; (6) normal pulmonary function, who could keep quiet and regular breathing after initial respiration training.

Table 1 Clinical data of the 7 patients with hepatocellular carcinoma

No.	Sex	Age (years)	Tumor location	Tumor size (cm)	Child-Pugh degree	Liver volume (cm^3)
1	Male	68	Right lobe	4.5×5.6	A	1 085.32
2	Male	40	Caudate lobe	6.0×7.3	A	1 288.64
3	Male	33	Caudate lobe	3.0×4.2	A	1 341.30
4	Male	39	Right lobe central	6.5×7.8	A	1 200.75
5	Male	56	Right lobe	7.4×8.5	A	1 182.17
6	Female	58	Right lobe	6.2×8.0	A	1 374.18
7	Female	58	Right lobe	3.3×4.8	B	1 232.36

Between October 2005 and June 2006, 7 HCC patients, 5 males and 2 females were included in this study at Cancer Center, Sun Yat-sen University, Guangdong. The median age was 56 years (range 33-68). The patients characteristics are shown in Table 1.

Immobilization and 4DCT scanning

All patients were positioned in the supine position with arms raised, immobilized with vacuum pillow.

The 4DCT scanning equipments were as follows: Discovery ST 16-slice PET/CT (General Electric Medical Systems), Advantage 4D (GE Medical Systems, Wankesha, WI), Real-Time Positioning Management Respiratory Gating System (Varian Medical Systems, Palo Alto, CA).

Patients were trained to keep quiet and regular breathing before CT simulation. The CT scanning slices were obtained from 3-4 cm above the diaphragm to the 4^{th} lumbar vertebrae, and the slice thickness was 2.5 mm for enhancement scanning.

A plastic box with a pair of reflective markers was placed on the patients midsection, where was the midway between the xiphoid and the umbilicus. The markers motion was captured by the infrared camera, and the respiratory signal was recorded synchronously with X-ray "on" signal from the CT scanner. The scanner was operated in an axial cine mode,

with multiple scans performed at each couch position for a duration of about 1-1.5 s longer than the length of the patients respiratory cycle. Data acquisition and radiation were turned off as the couch was advanced to the next scan position to begin data acquisition again. The whole time of CT scanning was about 90-120 s.

CT sorting and image registration

After 4DCT scanning, the GE software Advantage4D then was used to read all reconstructed images as well as the respiratory phases calculated by the RPM system. Each image from the acquired data set was sorted into one of 10 phase bins using the Advantage 4DCT application running on an Advantage Workstation 4.2 (General Electric Co., Waukesha, WI). The phase bins were, to a good approximation, evenly spaced in time over the respiratory cycle. The 10 exported respiratory phase volumes, evenly distributed over a respiratory cycle, were CT0%, CT10%, CT20%... CT50%... CT90%. CT0%, CT20% and CT50% corresponded to end-inhalation, mid-exhalation and midway between inhalation peaks, which were usually close to end-exhalation, respectively. All CT images were registered on three dimensional treatment planning system (3DTPS, Philips ADAC Pinnacle3 7.4f).

Target/ organ delineation

Target volumes are defined as follows: GTV represented the primary lesion visualized on CT images; CTV was defined as the GTV plus 1.0 cm margin, but confined to the edge of liver; ITV-4D derived from contouring of all 10 phases of CTVs; PTV-3D derived from a single CTV of 20% phase CT image plus conventional margins; PTV-4D derived from ITV-4D plus setup margins. In our hospital, the actual setup margin is about 5 mm. Conventional margins were defined as 0.7-1.0 cm in the mediolateral (LL) and ventrodorsal (AP) direction, 1.0-2.5 cm in the craniocaudal (CC) direction. To determine the CC margins, the diaphragmatic excursion by respiration was visualized fluoroscopically.

The organs at risk (OARs) included liver, kidneys, stomach, small intestine, and spinal cord. Normal liver volume was defined as the entire liver volume minus GTV.

GTVs and CTVs were manually contoured on all 10 phases of the 4DCT scan; OARs were contoured on the 20% phase CT image only. To eliminate interobserver variations, all the volumes were outlined by the same clinician using the same standard window/level settings.

Treatment planning

The 3D and 4D treatment plans were made for each patient using different PTVs: PTV-3D and PTV-4D. Both of the two plans were designed at the 20% breathing phase CT images using 3DTPS. 3DCRT was carried out by 8-MV or 15-MV photon linear accelerator (Elekta, Precise). With the help of beams eye view, multiple coplanar or noncoplanar fields were designed. The dose was prescribed to isocenter as 100% with inhomogeneity tissue correction, and PTV was calculated to cover 90% of the isodose curve. The treatment plans were interactively optimized based on dose distribution, dose volume histograms (DVH), Lyman-Kutcher-Burman normal tissue complication (NTCP) model, and Veff (Effective volume). The prescription doses were determined by the fraction of the normal liver receiving more than 50% of the isocenter dose and physicians own judgments, which included patient KPS and liver function. The total dose range was 5060 Gy/day, 2 Gy/time.

The three parameters of the Lyman NTCP model, TD50, n, and m, were cited Burman parameters [6], which are shown in Table 2.

Table 2 Normal tissue complication probability (NTCP) parameters values

Organ	TD50	n	m	End point
Liver	40	0.32	0.15	Liver failure
Kidney	28	0.70	0.10	Clinical nephritis
Stomach	65	0.15	0.14	Ulceration
Small intestine	55	0.15	0.16	Obstruction

TD50: the tolerance for a 50% complication; n: volume-effect parameter; m: steepness of the dose-response at TD50.

Quantitative evaluation

Target volumes: V95, V98, V100 etc: the target volume covered by the 95%, 98%, 100% isodose curve; Dmin: minimum dose; Dmax: maximum dose; Dmean: mean dose.

MDTNL: mean dose to normal liver; Livers V30, V40: volume included by 30, 40 Gy isodose curve; Livers V50%: volume included by 50% isodose curve; Kidneys V20, Dmean;

Stomachs V40, Dmean; Small intestines V40, Dmean.

Statistical analysis

The data were analyzed by the software of SPSS12.0. Comparison of the target volumes and dosimetric evaluation was tested by Paired-Samples T test.

Results

Comparison of target volumes

Table 3 presents volumes of CTV, ITV, PTV-3D, PTV-4D. The average volumes of PTV in the 3D and 4D plans were 417.6± 197.7cm^3, 331.9± 183.1cm^3, decreased by 85.68± 30.82 cm^3 or 20.5% (12.6%-34.4%) (P=0.000). The volumes of PTV-4D were smaller than those of PTV-3D in all patients. The volumes of PTV-4D were smaller than PTV-3D in all three dimensions for 5 patients, but, they exceeded PTV-3D in some slices for the other 2 patients. Figure1 and 2 show the comparison of PTVs between 3D and 4D plans of these 2 typical patients.

Table 3 Comparison of target volume for the 7 patients

No.	CTV-20%(cm^3)	ITV-4D(cm^3)	PTV-3D(cm^3)	PTV-4D(cm^3)
1	110.75	146.95	371.81	243.88
2	182.75	243.62	500.47	397.84
3	33.61	57.81	182.46	121.05
4	140.73	171.69	389.12	292.83
5	271.83	345.76	585.78	512.02
6	311.76	408.59	710.69	608.53
7	61.18	75.13	182.71	147.13
Mean	158.94	207.08	417.58	331.90

CTV, clinical target volume; ITV, internal target volume; PTV, planning target volume. t=7.356, P=0.000.

Dosimetric evaluation of target volumes

The dosimetric evaluation of PTV between 3D and 4D plans is shown in Table 4. There were no significant differences in PTV coverage and dose uniformity among the two plans because of similar designment of irradiating fields (P>0.05).

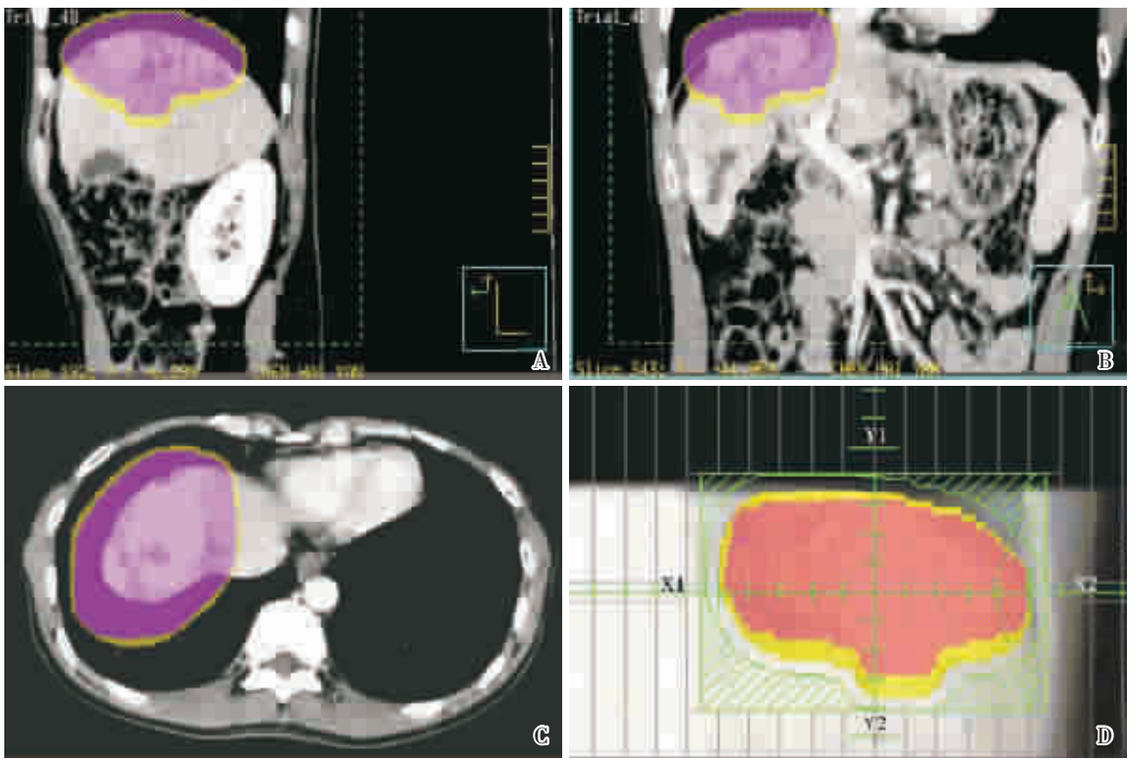

Figure 1 Comparison of planning target volumes (PTVs) between 3D and 4D plans for patient No. 4

A: sagittal view; B: coronal view; C: transverse view; D: digitally reconstructed radiograph.

The yellow area indicates PTV in 3D plans; the magenta area indicates PTV in 4D plan. PTV-4D is smaller than PTV-3D in all 3 dimensions for this patient.

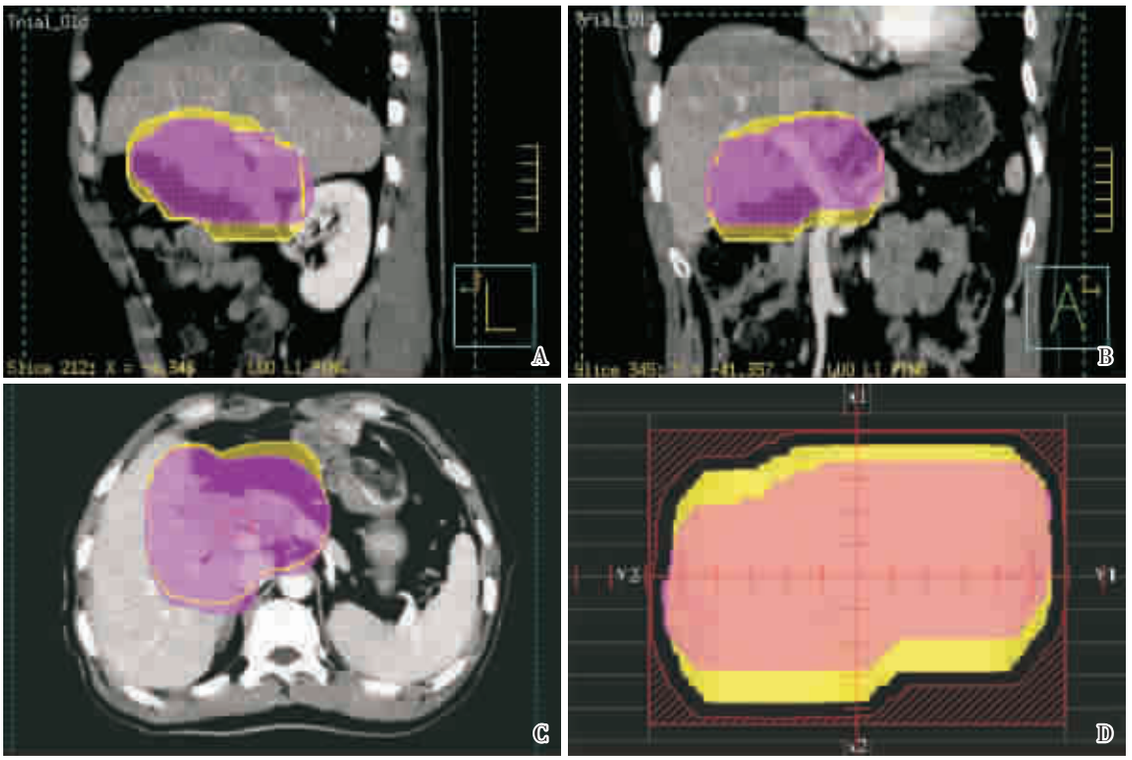

Figure 2 Comparison of PTVs between 3D and 4D plans for patient No. 2

A: sagittal view; B: coronal view; C: transverse view; D: digitally reconstructed radiograph. PTV-4D is larger than PTV-3D in some slices for this patient.

Table 4 Dosimetric comparison between 3D and 4D plans in planning target volumes

Item	3D plan	4D plan	*t* value	*P* value
V100(%)	45.47±18.66	41.10±17.45	1.23	0.265
V98(%)	80.78± 7.50	77.68± 8.92	2.33	0.059
V95(%)	96.19± 1.99	95.52± 2.55	2.26	0.064
D_{min}(Gy)	43.21± 3.37	43.99± 2.24	−1.05	0.333
D_{max}(Gy)	53.32± 1.51	52.99± 1.55	2.37	0.056
D_{mean}(Gy)	50.60± 1.31	50.49± 1.29	1.74	0.132

V100, V98, V95: volume included by 100%, 98%, and 95% isodose curves. D_{min}, minimum dose; D_{max}, maximum dose; D_{mean}, mean dose.

Dosimetric evaluation of OARs

Table 5 displays the dosimetric comparison between 3D and 4D plans in organs at risk. The 4D plans spared more normal liver, kidney, stomach and small intestine than 3D plans, especially for liver. Compared to 3D plans, the V30, V40, V50% decreased from 38.77%, 27.32%, 45.36% to 33.59%, 22.62%, 39.1%, respectively ($P<0.05$); MDTNL decreased from 24.13Gy to 21.5Gy in 4D plans ($P=0.003$); the mean doses to stomach were 12.38Gy and 11.90Gy in 3D and 4D plans ($P=0.011$). There were no statistical significances in the dosimetric comparison of unilateral kidneys and small intestine. Figure 3A shows the dose volume histogram comparison for normal tissues between the two plans when the prescription dose was 50Gy.

Comparison of NTCP and dose escalation

Table 5 Dosimetric comparison between 3D and 4D plans in organs at risk

Item	Plan-3D	Plan-4D	*P* value
Mean dose to normal liver (Gy)	24.13± 7.61	21.50± 8.30	0.003
Liver's V30 (%)	38.77±19.92	33.59±20.71	0.001
Liver's V40 (%)	27.32±13.63	22.62±13.40	0.000
Left kidney's V20 (%)	2.90± 4.96	1.36± 2.34	0.271
Left kidney's D_{mean} (Gy)	2.22± 2.20	1.74± 1.87	0.151
Right kidney's V20 (%)	17.84±16.54	13.42±11.50	0.113
Right kidney's D_{mean} (Gy)	8.24± 6.84	6.69± 5.19	0.151
Stomach's V40 (%)	4.23± 8.99	3.35± 7.22	0.241
Stomach's D_{mean} (Gy)	12.38± 9.67	11.90± 9.41	0.011
Small intestine's V40(cm^3)	7.89± 8.33	5.87± 6.01	0.085

V30, V40, V20: volume included by 30, 40, and 20 Gy isodose curves.

Table 6 displays the NTCP and Veff comparison between 3D and 4D plans in several normal tissues. The NTCP and Veff of liver decreased from 21.57%, 25.47% to 15.86%, 21.97%, respectively. The NTCP of left kidney and stomach were 0 because of low irradiation in both plans. There were no significant differences in NTCP of right kidney and small intestine in the two plans. Under the circumstance of not increasing NTCP, the 4D plans allowed for the increase of calculated dose from 50.57± 1.51Gy to 54.86± 2.79Gy (P=0.003), average 9.72%（4%-16%, Figure 4）. Figure 3B shows the dose volume histogram comparison for normal tissues of the same patient between the two plans when the prescription dose of 4D plan was escalated to 58Gy.

Table 6 NTCP and Veff comparison of normal tissues

Item	3D plan	4D plan	*P* value
Liver's NTCP	21.57±20.47	15.86±18.59	0.002
Liver's Veff	25.47±11.31	21.97±11.74	0.001
Left kidney's NTCP	0	0	
Right kidney's NTCP	0.29± 0.49	0	0.172
Stomach's NTCP	0	0	
Small intestine's NTCP	3.29± 5.06	1.86± 2.85	0.140

NTCP, normal tissue complication probability; Veff, effective volume.

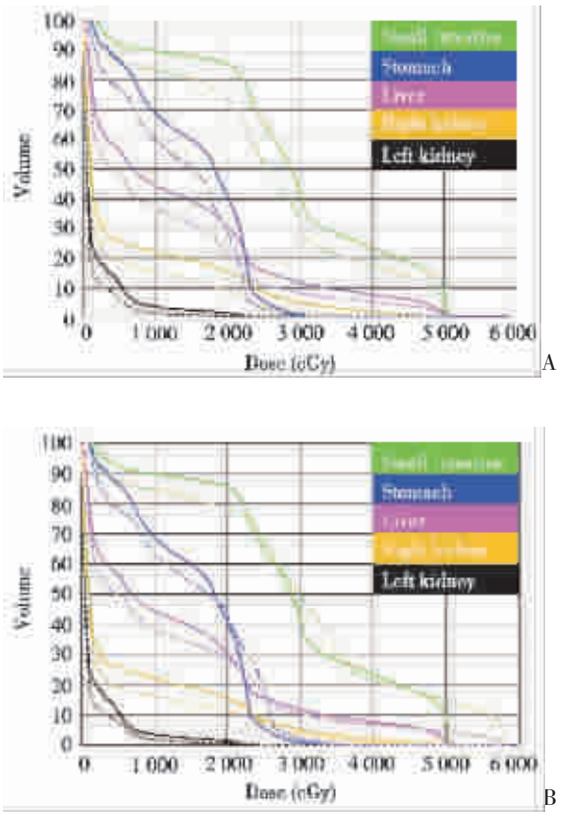

Figure 3 Dose-volume histogram comparison of 3D plan (solid lines) and 4D plan (dashed lines) for the normal tissues of patient No. 3

A: Prescription dose are 50 Gy for both plans.

B: The prescription dose of 4D plan is escalated to 58 Gy.

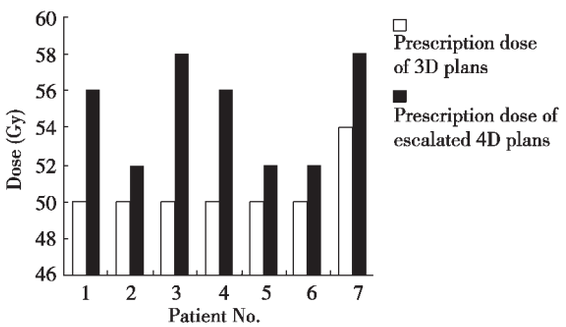

Figure 4 Dose escalation for 4D plans

Discussion

The role of radiation therapy in HCC is limited because of the low whole-liver tolerance to radiation and difficulty with tumor location with respiration. With the introduction of three-dimensional conformal radiotherapy, a portion of normal surrounding tissues could be excluded from the treatment volume and dose conformality has been improved. The rationale of 3D CRT is to escalate the radiation dose to enhance tumor control without irradiating more normal tissues. Internal organ motion with respiration is a significant problem in the treatment of both thoracic and abdominal malignancies. Accurate targeting of liver tumor is difficlt even with the technique of 3D CRT. Shimizu et al.[7] reported the movement of liver using high-speed magnetic resonance: (5.2± 1.8)mm in the LL direction, (4.6± 1.6)mm in the AP direction, (10.6± 7.0)mm in the CC direction, respectively. Sufficient margins should be added to CTV to ensure the full dose coverage of target volume throughout the treatment course. The most common method to acquire geometric margins is fluoroscopy. However, fluoroscopy can only observe the movement of diaphragm in CC direction approximately, which could not measure the movement in LL and AP direction. Some data

have reported that the movement of liver is not accord with the motion of diaphragm [8,9]. Thus such margins derived from fluoroscopy are not accurate. How to accurately define target volume of liver tumor is becoming increasingly important.

4D CT data comprise explicitly patient-specific respiratory motion into treatment planning to ensure dose coverage of the target throughout the breathing cycle [10-13]. Compared to helical CT, 4DCT can generate accurate ITV, which covers the movement range of tumor [14]. As shown in this study, the average volume of PTV-4D was (85.68 ± 30.82) cm^3, smaller than PTV-3D in all 7 patients. But the specific information of every patient was not identical. Figure 1 shows that the volume of PTV-3D comprises PTV-4D in all three dimensions (389.12 cm^3 & 292.83 cm^3). This indicates that the tumor motion is smaller than expected in 3D plan, so there normal tissues could be unnecessarily irradiated, especially for liver and right lower lobe of lung. Figure 2 presents another case, showing that though the volume of PTV-4D is smaller than PTV-3D (500.47 cm^3 & 397.84 cm^3), it exceeds the latter in some slices This indicates that the PTV-3D not only overly covers, but also geometrically misses the target volume. The movement of diaphragm can be considered as the largest movement of liver in the whole breathing cycle. To avoid geometric miss, the CC margins are usually defined according to the largest movement, resulting in the over coverage of the target volume. The LL and AP margins are usually derived from experience of clinicians, which can not be measured by conventional methods. A geometric miss is still possible if tumor motion is greater than the assumed motion. The study demonstrated that the 3D plans have pitfalls of geometric miss or over coverage of target volume.

Because of the accurate definition of target volume, the PTV reduction may allow for sparing of normal tissues or for dose escalation with stable normal tissue complication. Our data displayed that the 4D plans spared more normal liver, kidney, stomach and small intestine than 3D plans, especially for liver. Compared to 3D plans, MDTNL decreased from 24.13Gy to 21.5Gy in 4D plans (P= 0.003); the NTCP and Veff of liver decreased from 21.57%, 25.47% to 15.86%, 21.97%, respectively. Under the circumstance of not increasing NTCP, the 4D plans allowed for increasing calculated dose average 4.29 ± 2.43Gy, average 9.72% (4%-16%). As shown in Figure 3, MDTNL were 12.99Gy and 10.37Gy in 3D and 4D plans when the prescribed dose were 50Gy; when the prescribed dose of 4D plan escalated to 58Gy, MDTNL was 12.03Gy, which was still lower than 3D plan. Investigations have demonstrated a dose-response relationship in localized radiotherapy for liver cancers with better response rates and prolonged hepatic control in groups that received higher RT doses [15-16]. Park et al. [17] reported the existence of a dose-response relation with a total of 158 HCC patients treated with local RT. An objective response was observed in 106 patients, showing a response rate of 67.1%. The mean radiation doses were 50.1 ± 6.6 Gy in the responders and 44.3 ± 9.0 Gy in the nonresponders. The response rates in patients treated with doses < 40Gy, 40-50 Gy, and >50 Gy were 29.2% , 68.6% , and 77.1% , respectively. Statistical analysis revealed that the total dose was the most significant factor associated with the tumor response. Thus, the dose escalation based on 4D plans can elevate the tumor response rate and prolong the overall survival in theory.

The irradiated volumes of left kidney, stomach, and small intestine were limited because of the tumor location of the 7 patients in either right or caudate lobe of the liver. There was no statistical significance in the dosimetric comparison, though the doses to these tissues in 4D plans were decreased compared to 3D plans.

The Lyman model is one of the widely used models to predict the normal tissue complication probability. The three parameters contained in this model of liver were influenced by many factors, including Child-Pugh class, treatment methods, a primary hepatobiliary cancer diagnosis vs. liver metastases, gender, et al. The parameters reported by each research were different [18-20]. The cited Burman parameters in our study could not predict the absolute probability of normal tissue complication, so the data were only used as references to optimize and compare the treatment plans.

In conclusion, the conventional 3D plan has

shortages of geometric miss or over coverage of target volume. The 4DCT-based plan can accurately define target volume to spare more normal tissues and make dose escalation compared with 3D CRT. In theory, the 4D plan can elevate the tumor response rate and decrease NTCP, especially for radiation-induced liver disease. Hence, further clinical trial is necessary to determine whether 4DCT-based plan can increase tumor regression and prolong survival.

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