A comparative study of four-dimensional cone beam computed tomography (4DCBCT) and three-dimensional cone beam computed tomography (3DCBCT) guided treatment setup in liver cancer radiotherapy

Bao Wan
Chinese Academy of Medical Sciences & Peking Union Medical College
Lingxia Xin
Chinese Academy of Medical Sciences & Peking Union Medical College
Yanxin Zhang
Chinese Academy of Medical Sciences & Peking Union Medical College
Deqi Chen
Chinese Academy of Medical Sciences & Peking Union Medical College
Zhuoran Li
Chinese Academy of Medical Sciences & Peking Union Medical College
Yuan Zong
Chinese Academy of Medical Sciences & Peking Union Medical College
Bofei Liu
Chinese Academy of Medical Sciences & Peking Union Medical College
Wenhua Qin
Chinese Academy of Medical Sciences & Peking Union Medical College
Zhiwei Zhang
Chinese Academy of Medical Sciences & Peking Union Medical College
Yongtai Zheng
Chinese Academy of Medical Sciences & Peking Union Medical College
Yirui Zhai
Chinese Academy of Medical Sciences & Peking Union Medical College
Bo Chen (cboo8778@126.com)
Chinese Academy of Medical Sciences & Peking Union Medical College

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Research Article

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Abstract

Background and purpose

To compare the setup errors and the clinical target volume (CTV) to planning target volume (PTV) margins in image-guided radiotherapy (IGRT) for liver cancer using three-dimensional cone beam computed tomography (3DCBCT) and four-dimensional cone beam computed tomography (4DCBCT), and explore the advantages of 4DCBCT for the position verification in liver cancer irradiation.

Materials and methods

Fifty-five patients with liver cancer were enrolled. All patients' CT, four-dimensional computed tomography (4DCT) and Magnetic Resonance (MR) simulation images were collected. Image registration, target delineation, and plan design were accomplished in Pinnacle treatment planning system. Pre-treatment's 3DCBCT and 4DCBCT images were collected at a certain frequency and registered with the simulation CT images. Before beam delivery, the therapy couch was corrected based on the setup errors measured by 4DCBCT. Investigators recorded the setup errors and calculated the CTV to PTV margins using van Herk's formula. Paired t-test was used to compare the difference of the two groups.

Results

A total of 452 sets of 3DCBCT and 4DCBCT images were collected. The setup errors in 4DCBCT group in superior-inferior (S-I) direction, anterior-posterior (A-P) direction, transverse plane, and coronal plane were significant smaller than in 3DCBCT group, which were 2.6 ± 4.8 mm and 2.1 ± 4.0 mm, $P < 0.001$; 1.8 ± 1.9 mm and 1.4 ± 1.7 mm, $P < 0.001$; 0.80 ± 0.76° and 0.75 ± 0.61°, $P < 0.001$; 0.90 ± 0.74° and 0.78 ± 0.75°, $P < 0.001$. And the CTV-PTV margins in three-dimensional directions are (5.7, 9.8, 5.8) mm and (5.1, 8.0, 4.6) mm, respectively.

Conclusion

4DCBCT is superior to 3DCBCT in monitoring setup errors and supports smaller PTV margins for liver cancer radiotherapy.

INTRODUCTION

The incidence rate and mortality rate of liver cancer ranked sixth and third respectively in the world (1). The commonly used treatment strategies for liver cancer include surgery, transcatheter arterial interventional therapy, radiotherapy, radiofrequency ablation and systematic therapy, etc. (2). With the development of radiotherapy technology, especially the development of the image-guided intensity modulated radiotherapy (IMRT) technology, the safety and efficacy of radiotherapy for liver cancer have been confirmed (3). Previous studies reported that the prescribed dose was significantly and positively correlated with the survival rate and response rate of patients with liver cancer (4). However, respiratory movement, cardiac movement, gastrointestinal peristalsis, tumor shrinkage and other factors cause geometric uncertainty between the inter-fractional and intra-fractional setup in liver cancer irradiation, which limits the precision radiation dose delivered to tumor. Therefore, accurate position verification is one of the premises of accurate liver cancer irradiation.

At present, three-dimensional cone beam computed tomography (3DCBCT) technology is widely used in image-guided radiotherapy (IGRT)(5). Although previous study found that 3DCBCT was adequate for monitoring the lipiodol-guided stereotactic radiotherapy for liver cancer(6), 3DCBCT scanning time covers several of respiratory cycles and obtains indefinite tumor margins. And previous study reported that automatic registration outcomes based on 3DCBCT were poor during lung cancer irradiation(7). In addition, 3DCBCT has weakness in monitoring organs at risk (OARs) and tumor motion, limiting its application in the clinical practice. In contrast, four-dimensional cone beam computed tomography (4DCBCT) can monitor the motion of target and OARs, which has potential advantages over 3DCBCT in evaluating the spatial position of tumors and OARs. In addition, accurately expanding the clinical tumor volume (CTV) to the planning target volume (PTV) is one of the prerequisites for precise radiotherapy of liver cancer, which can improve the local control rate and decrease the risk of radiation induced liver disease.

This study retrospectively analyzed and compared the differences between 4DCBCT and 3DCBCT in liver irradiation setup, and discussed the feasibility of 4DCBCT for the position verification in liver cancer radiotherapy.

MATERIALS AND METHODS

Patients

Fifty-five patients with liver cancer who received radiotherapy in Department of Radiation Oncology, ***, between January 2021 and June 2022 were included. The eligibility criteria included: (1) clinical or pathological diagnosis of primary liver cancer; (2) KPS ≥ 70 and tolerating radiotherapy; (3) the immobilization devices of thoracoabdominal flat (CIVCO, Medical Solutions, Orange City, Iowa); (4) keeping regular respiration after breathing training; (5) receiving both 3DCBCT and 4DCBCT scan before treatment. This study was in accordance with the Declaration of Helsinki. The clinical characteristics was shown in Table 1. The median age of enrolled patients was 60 (range, 31 ~ 78) years. 53 (96.4%) patients were diagnosed with hepatocellular carcinoma (HCC), and 2 (3.6%) patients with intrahepatic cholangiocarcinoma (ICC). Lesions located in right hepatic lobe were found in 42 (76.4%) patients. The median tumor size was 7.4 (range, 1.3 ~ 14.6) cm. 48 (87.3%) patients were infected with Hepatitis B, and 5 (9.1%) with Hepatitis C. 43 (78.2%) patients were at Barcelona Clinic Liver Cancer (BCLC) C stage.

Table 1
Demographics.

Characteristics	No.	%	Characteristics	No.	%
Sex			**Tumor size (cm, median, range)**	7.40 (1.3 ~ 14.6)	
Male	49	89.1	**Number of lesions**		
Female	6	10.9	Single	29	52.7
Age (years, median, range)	60 (31 ~ 78)		Multiple	26	47.3
ECOG	0 ~ 1		**Stage (AJCC, 8th ed.)**		
Tumor position			a	3	5.5
Left hepatic lobe	10	18.2	b	3	5.5
Right hepatic lobe	42	76.4	a	3	5.5
Hepatic junction of left and right lobes	3	5.5	b	0	0
Child-Pugh Class			a	3	5.5
A5	47	85.5	b	28	50.9
Etiology			a	3	5.5
None	2	3.6	b	12	21.8
Hepatitis B	48	87.3	**BCLC stage**		
Hepatitis C	5	9.1	C stage	43	78.2
Pathology			**Prescribed dose (Gy)**	58(40 ~ 60)	
HCC	53	96.4	**No. fractions**	23(10 ~ 25)	
ICC	2	3.6	**Technology**		
CHC	0	0	VMAT	55	100

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; CHC, combined hepatocellular-cholangiocarcinoma; AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; Gy, Gray; VMAT, volume modulated arc radiotherapy.

CT and MR simulations

For fasting four hours, all patients took orally 300 ml contrast agent 15 minutes before CT simulation. Laying on a CT simulator (Philips Brilliance Big Bore or Siemens SOMATOM Definition AS 40), patients were immobilized with thermoplastic body membrane (Claridi, Guangzhou, China) in supine position with both arms above the forehead and the right hand over left, and underwent free-breathing contrast-enhanced CT (CECT) scanning (scanning conditions: 120kV, 150mAs; scanning thickness and spacing were 5 mm), with the scanning range up to the supraclavicular area, down to the L5 cone. After that, 4DCT scanning was performed under the free breathing state. And a total of 10 respiratory phases (0%~90%) were acquired. All patients underwent magnetic resonance (MR) simulation the next day. The CT and MR simulation images were transferred to the Pinnacle treatment planning system (version 9.10, Philips, the Netherlands) through the MOSAIQ network system (MEKODA, Sweden) for target delineation and plan design.

Target delineation

Gross tumor volume (GTV) was the primary tumor in CECT and MRI image. The GTV-CTV margins were 5 mm in all directions and 10-15mm in the direction of blood vessels with tumor thrombus. The CTV-PTV margins were 5 mm in anterior-posterior (A-P) and left-right (L-R) directions, and 10 mm in superior-inferior (S-I) direction, referring to the 4DCT image. OARs were also delineated, including normal liver tissue, esophagus, stomach, duodenum, bowels, left kidney, and spinal cord. The prescription dose was 40 ~ 60Gy in 20 ~ 30 fractions. All patients were treated with volume modulated arc radiotherapy (VMAT) technology.

Guidance image acquisition, registration and treatment procedure

Before beam delivery, all the enrolled patients underwent 3DCBCT (scanning parameters: 120KV, 25mAs, S20, F0, scanning thickness and spacing were 3 mm, scanning angle from − 180 degree to 20 degree) and 4DCBCT scanning (scanning parameters: 120KV, 25mAs, S20, F0, scanning thickness and spacing were 3 mm, scanning angle from − 180 degree to 20 degree) under the state of free breathing with XVI Symmetry respiratory management system (Infinity linear accelerator, Elekta, Sweden). The scanning frequency was once a day in the first week, and then once a week. The scanning scope of the liver registration frame included the upper and lower boundaries (5cm) of the entire liver area, the front boundary to the outer edge of the skin, the rear boundary to the posterior edge of the cone, the inner boundary to the lateral edge of the left kidney, and the outer boundary to the outer edge of the skin. The same registration frame was used for the two types of scans. The Clipbox registration was performed between 3DCBCT images and simulation CT images. The registration method between 4DCBCT images and simulation CT images was mainly based on 4D gray scale translation of Mask. Both registration methods were supplemented by manual fine adjustment. The six-dimensional setup errors of the two groups in L-R direction, S-I direction, A-P direction, sagittal plane, transverse plane, coronal plane were obtained. The couch was corrected based on the setup errors measured by 4DCBCT, and then the treatment was carried out.

Definition of setup errors and CTV-PTV margin calculation

Systematic setup error (Σ) is defined as the standard deviation of the average setup error of all patients. Random setup error (σ) is defined as the root mean square of the standard deviation of setup error of individual cases (8, 9).

Specifically, the setup error calculation steps are: (1) record the setup errors and the number of fractions of each patient; (2) calculate the mean value m_k of setup errors of all fractions for each patient; (3) calculate the average setup error $M(m_k)$ of all patients; (4) calculate the standard deviation $\Sigma(m_k)$ of the average setup errors using:

$$\Sigma\left(m_k\right)=\sqrt{\frac{\sum n_k\left(m_k-M\left(m_k\right)\right)^2}{N-1}}$$

where n_k is the number of fractions of the *kth* patient, and N is total number of fractions of all patients; (5) calculate the standard deviation S_k of setup errors of all fractions in each case; (6) calculate the root mean square $\sigma(S_k)$ of the standard deviation of setup errors of all patients using:

$$\sigma\left(S_k\right)=\sqrt{\frac{\sum\left(S_k\right)^2}{N-1}}$$

The CTV-PTV margin were calculated using the van Herk formula(10):

$$M_{PTV}=2.5\sum\left(m_k\right)+0.7\sigma\left(S_k\right)$$

Statistical analysis

SPSS Statistics (v25.0; IBM, Armonk, NY) software was used to conduct paired-t test for comparing the setup errors of the 3DCBCT and 4DCBCT groups, with the significant level of 0.05 (two side).

RESULTS

Setup errors

Totally 452 pairs of 3DCBCT and 4DCBCT scans were acquired. The setup errors measured using 3DCBCT and 4DCBCT after automated correction and manual correction were shown in Table 2. The setup errors of 4DCBCT group in S-I direction, A-P direction, transverse plane, and coronal plane were significant smaller than 3DCBCT group. The setup errors (mean ± std) in 3DCBCT and 4DCBCT groups were: L-R direction: 1.7 ± 2.0 mm and 1.5 ± 1.9 mm, $P = 0.7$; S-I direction: 2.6 ± 4.8 mm and 2.1 ± 4.0 mm, $P < 0.001$; A-P direction: 1.8 ± 1.9 mm and 1.4 ± 1.7 mm, $P < 0.001$; sagittal plane: 0.91 ± 0.65° and 0.73 ± 0.60°, $P = 0.667$; transverse plane: 0.80 ± 0.76° and 0.75 ± 0.61°, $P < 0.001$; coronal plane: 0.90 ± 0.74° and 0.78 ± 0.75°, $P < 0.001$.

Table 2
Translational and rotation setup errors using 3DCBCT and 4DCBCT after registration.

	3DCBCT	4DCBCT	T statistic	P value
L-R (mm)	1.7 ± 2.0	1.5 ± 1.9	-0.386	0.700
S-I (mm)	2.6 ± 4.8	2.1 ± 4.0	-8.979	< 0.001*
A-P (mm)	1.8 ± 1.9	1.4 ± 1.7	11.516	< 0.001*
Sagittal plane (°)	0.91 ± 0.65	0.73 ± 0.60	0.431	0.667
Transverse plane (°)	0.80 ± 0.76	0.75 ± 0.61	-10.354	< 0.001*
Coronal plane (°)	0.90 ± 0.74	0.78 ± 0.75	-6.943	< 0.001*

L-R, left-right direction; S-I, superior-inferior direction; A-P, anterior-posterior direction; 3DCBCT, three-dimensional cone beam computed tomography; 4DCBCT, four-dimensional cone beam computed tomography; *, statistically significance.

Distribution of setup errors

The distributions of translational and rotational setup errors of 3DCBCT and 4DCBCT groups were shown in Table 3 and Table 4, respectively. The proportion of distribution of translation setup errors (< 4mm) was higher in 4DCBCT group versus 3DCBCT group in L-R, S-R, and A-P directions, with the proportion of 91.37%, 61.50%, and 90.49% versus 86.50%, 55.53%, and 87.61%, respectively. The setup errors in S-I direction were more significant than L-R and A-P directions in both groups. The proportion of distribution of rotational setup errors (≤ 1°) was higher in 4DCBCT group versus 3DCBCT group in sagittal plane and coronal plane, with a proportion of 73.23% and 71.68% versus 67.48% and 65.27%, respectively. The setup errors (> 2°) in transverse plane were more significant than sagittal plane and coronal plane in both groups, with the proportion of 14.60% and 14.16%, respectively.

Table 3
The distribution of translational setup errors of 3DCBCT and 4DCBCT groups.

Group	3DCBCT				4DCBCT			
Error (mm)	< 4.0	4.0 7.0	7.0 10.0	> 10.0	< 4.0	4.0 7.0	7.0 10.0	> 10.0
L-R (%)	86.504	12.168	1.328	0.000	91.372	7.301	1.106	0.221
S-I (%)	55.531	24.336	11.726	8.407	61.504	23.451	11.947	3.097
A-P (%)	87.611	11.504	0.664	0.221	90.487	8.186	1.106	0.221

L-R, left-right direction; S-I, superior-inferior direction; A-P, anterior-posterior direction; 3DCBCT, three-dimensional cone beam computed tomography; 4DCBCT, four-dimensional cone beam computed tomography.

Table 4
The distribution of rotational setup errors of 3DCBCT and 4DCBCT groups.

Group	3DCBCT			4DCBCT		
Error (°)	≤ 1	1 2	≥ 2	≤ 1	1 2	> 2
Sagittal plane (%)	67.478	21.681	10.841	73.230	21.681	5.088
Transverse plane (%)	63.274	22.567	14.159	48.894	36.504	14.602
Coronal plane (%)	65.265	24.779	9.956	71.681	20.354	7.965

3DCBCT, three-dimensional cone beam computed tomography; 4DCBCT, four-dimensional cone beam computed tomography.

CTV-PTV margins

The CTV-PTV margins calculated based on 4DCBCT were smaller than that of 3DCBCT, which were 5.1 mm, 8.0 mm and 4.6 mm versus 5.7 mm, 9.8 mm, 5.8 mm in L-R, S-I, A-P directions.

DISCUSSION

At present, 3DCBCT technology is still widely used for location verification in clinical practice. However, a complete 3DCBCT scan include multiple respiratory phases, resulting in motion artifacts (11). However, 4DCBCT takes into account the time weighted average factor on the basis of 3DCBCT, which can display the position of tumor and surrounding normal organs throughout the respiratory cycle, track the longest dwell stage of tumor in the complete respiratory phase, and more accurately guide the setup error correction (12). 4DCBCT can dynamically observe 10 groups of setup errors under 10 respiratory phases in the complete respiratory cycle, and obtain the final setup errors through time weighted average, so as to improve the accuracy and ensure the efficacy of radiotherapy.

Many studies have shown that 4DCBCT has potential advantages in stereotactic radiotherapy of lung cancer. It can monitor the spatial position information and motion range of tumors, guide setup error correction, and support smaller CTV-PTV margin (13). Previous studies have reported that the setup errors measured based on 4DCBCT scan were smaller than that on 3DCBCT scan during lung cancer irradiation. Similarly, the location of liver tumors is easily affected by diaphragm movement, respiratory movement, gastrointestinal peristalsis, etc., and 4DCBCT also has potential advantages in monitoring the target motion in the radiotherapy of liver cancer. However, few studies have reported the application of 4DCBCT in the radiotherapy of liver cancer. Vergalasova et al. found that even with implanted markers, 3DCBCT scanning under free breathing state might not be accurate enough in guiding liver stereotactic radiotherapy (14). Our study first explored the feasibility and potential advantages of 4DCBCT in IGRT for liver cancer. This study found that the overall setup errors based on 4DCBCT measurement were smaller than 3DCBCT, especially in S-I direction, A-P direction, transverse plane, and coronal plane. In addition, the setup errors in S-I direction were more diverse in 4DCBCT group and 3DCBCT group, with 3.1% and 8.4%

of patients with setup errors more than 10mm, respectively. Thus, 4DCBCT is essential for monitoring the setup errors in S-I direction. And we believe that 4DCBCT is superior to 3DCBCT in monitoring the setup errors during liver cancer irradiation.

We also found that the CTV-PTV margin guided by 4DCBCT could be smaller than 3DCBCT, which should be beneficial to normal liver tissue sparing while ensured the target dose coverage, and thus better ensure the safety and efficacy of radiotherapy for patients with liver cancer. The error in liver cancer radiotherapy has multiple sources, such as irregular respiratory motion, poor posture repetition, and other motion during treatment. These variances may affect the dose distribution in the target area and endanger normal tissues. Most of the selected patients in this study were patients with stage III liver cancer. The median size of the tumor was 7.6 cm. 87.3% of the patients were infected with chronic hepatitis B virus. Therefore, it was more necessary to reduce the radiation dose exposing on the normal liver tissue to avoid the occurrence of radiation liver disease. Although the CTV-PTV margins may be insignificant comparing to “supermassive” liver tumors, it may play an important role in SBRT for liver cancer under free breathing and its value should be further explored.

In terms of time cost, it took 4 minutes for acquisition and high-resolution reconstruction of 4DCBCT images, and 1 min for image registration. Although the scanning time of 4DCBCT was averagely 62s longer than that of 3DCBCT, it could online evaluate the range of tumor motion and OARs to avoid the occurrence of target missing and unexpected OARs exposure. Compared with the overall treatment time, the increased position verification time is acceptable. Currently, several studies have focused on reducing 4DCBCT scanning time(15).

Our study has two advantages in design. First, the patients were scanned consecutively with 3DCBCT and 4DCBCT after setup, which minimized the interference of other unrelated factors, and could more accurately evaluate the difference between the setup errors measured by the two image guidance methods. Second, the 3DCBCT and 4DCBCT used in this study are widely used image guidance systems for Elekta linear accelerator, making our findings valuable in guiding the clinical practice of liver cancer radiotherapy.

This study also has limitations. First, this study is a single center study, and the accuracy of treatment setup depends on the skill and experience of the stuff. Therefore, the results of this study (such as setup errors and CTV-PTV margins) might not be well generalized to other centers without an extension multi-center study. Second, the number of enrolled cases was small, and no hierarchical analysis was conducted on tumor size and location, etc. Third, this study did not compare the differences in dosimetry distribution, local control and adverse events between the two groups. Fourth, the motion track of the lesions and surrounding OARs in six dimensional directions should be further explored.

CONCLUSIONS

We found that 4DCBCT is superior to 3DCBCT in monitoring setup errors in liver cancer irradiation. We also found that the CTV to PTV margins were smaller using 4DCBCT than that from 3DCBCT. 4DCBCT as a golden standard for the position verification in liver cancer irradiation should be recommended.

Abbreviations

3DCBCT, three-dimensional cone beam computed tomography; 4DCBCT, four-dimensional cone beam computed tomography; IGRT, image-guided radiotherapy; MR, magnetic resonance; GTV, gross tumor volume; CTV, clinical tumor volume; PTV, planning target volume; OARs, organs at risk; IMRT, intensity modulated radiotherapy; VMAT, volume modulated arc radiotherapy; L-R, left-right; A-P, anterior-posterior; S-I, superior-inferior; AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; Gy, Gray; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; CHC, combined hepatocellular-cholangiocarcinoma; CECT, contrast-enhanced CT

Declarations

Ethical Approval and Consent to participate

This study was approved by the ethics committee or institutional review board (approval number: 22/094-3295). And this study was a retrospective study and exempted from obtaining informed consent.

Consent for publication

All authors approved the version to be published.

Availability of supporting data

The data that support the findings of this study are available on request from the corresponding author.

Competing interests/Authors' contributions

The authors have declared no conflicts of interest. Bao Wan and Ling-Xia Xin drafted the paper for important intellectual content. Yan-Xin Zhang, De-Qi Chen, Zhuo-Ran Li, Yuan Zong, Bo-Fei Liu, Wen-Hua Qin, Zhi-Wei Wang, and Yong-Tai Zheng had substantial contributions to the conception or design of the paper, the acquisition, analysis, and interpretation of data for the paper. Bo Chen and Yi-Rui Zhai revised it critically. All authors approved the version to be published.

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