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Original Article

A comparative study of four- and three-dimensional computed tomography simulation in determining displacement and volume for target region of primary tumor in esophageal carcinoma

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Abstract: The current study aimed to compare internal gross target volume (IGTV) and its displacement of primary esophageal carcinoma based on four- and three-dimensional computed tomography (4D-CT and 3D-CT) simulation technology. Twenty-two esophageal carcinoma patients proved by pathology examination were included in this prospective study. Each patient sequentially received contrast enhancement free-breathing 3D-CT and respiration-synchronized 4D-CT simulation chest scan. The target volume and displacement in three orthogonal dimensions of three different IGTVs planning methods (including $IGTV_{4D}$, $IGTV_{4D'}$ and $IGTV_{3D}$) were obtained, followed by the calculation of dice similarity coefficient (DSC) and overlap index (OI) between $IGTV_{4D}$ and $IGTV_{4D'}$ $IGTV_{4D}$ and $IGTV_{3D}$ respectively for different segments of carcinoma. Statistical analysis was made through the Friedman test, variance analysis on repeated measurement data and paired-samples student t test and the difference was regarded as of statistical significance when $P < 0.05$. There was statistical significance of displacement at left-right, anterior-posterior, and superior-inferior directions of primary esophageal tumor GTV of the ten phases originated from medium-thoracic segments and medium-lower-thoracic segments ($P = 0.005$ and $P = 0.001$). There presented a significant difference of primary tumor volume where appeared $IGTV_{3D} > IGTV_{4D} > IGTV_{4D'}$ ($P < 0.05$). In other words, the implementation of GTV by means of extending position based on 3D-CT imaging would lead to unnecessary radiation of the surrounding normal tissues (about 9-24%); However, the application of GTV only by means of integrating end-inhalation and end-exhalation phases would result in uncover target area (about 10-34%). 4D-CT simulation technology is superior to 3D-CT simulation technology for Intensity Modulated Radiation Therapy (IMRT) in esophageal cancer.

Keywords: Esophageal carcinoma, four-dimensional computed tomography simulation, three-dimensional computed tomography simulation, comparative study

Introduction

Accurate simulation technology method is an important guarantee for Intensity Modulated Radiation Therapy (IMRT). Four-dimensional computed tomography (4D-CT) simulation is new technology used in thoracic and abdominal tumors simulation in recent years. Based on 3D computed tomography (3D-CT), through combining time factor, it uses respiratory phase registration technology for CT image capture and reconstruction. The current study aimed to compare internal gross target volume (IGTV) and its displacement of primary esophageal carcinoma based on 4D-CT and 3D-CT simulation technology, and to evaluate advantages of 4D-CT in esophageal carcinoma radiotherapy simulation.

Material and methods

General clinical data

A total of 22 patients newly diagnosed with esophageal carcinoma received by Radiotherapy Dept. of our hospital (grade A and class 3 special hospital) from May to October 2015 were included in this prospective study. All the enrolled patients voluntarily accepted 4D-CT simulation scanning. Twenty-two patients were diagnosed with esophageal squamous cell carcinoma, including 16 men and 6 women, at median age of 63 years old (41 to 87 years old). Exclusion criteria included the followings: be allergic to iodic contrast medium; esophageal lesion not obvious through CT enhancement scan.

The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of our hospital. Written informed consent was obtained from all participants.

CT simulation scanning

Respiratory training: Before CT simulation, each patient was conducted with respiratory training to remove tension as far as possible.

Positioning and marking: adopt supine position, select suitable headrest according to length of neck of patients and place two hands at both sides of body. Adopt thermoplastic film for neck and shoulder for postural immobilization. Make bellyband used for respiratory triggering fixed at inferior margin in patient's costal arch, and perform CT scanning when patient's breathing curve is relatively stable.

CT imaging device, parameters and methods: Adopt Philips's Brilliance Pinnacle 3 16-detector row spiral CT in this study. CT imaging parameters included 120 kV and 280 mAs, screw pitch of 2 mm, as well as layer thickness of 3 mm for both image scanning and reconstruction. Scanning scope ranged from upper edge of the second cervical vertebral body to lower edge of the fourth lumbar body. Before scanning, use high pressure injector to inject nonionic isotonic contrast medium 100 ml iohexol (Yangtze River Pharmaceutical Group, Jiangsu, China) with concentration of 30% at the speed of 3 ml/s through vein of arm, firstly complete conventional 3D-CT simulation enhancement scan under the state of quiet breathing; then immediately carry out 4D-CT simulation enhancement scan with time starting scanning lying between 120 and 180 seconds.

4D-CT image acquisition: Post-processing workstation software used information of respiratory movement to be integrated into 4D-CT image data, to reconstruct CT image for ten respiratory time phases in respiratory cycle, which were respectively named as T_0, T_1, T_2, T_3, T_4, T_5, T_6, T_7, T_8 and T_9, wherein, T_0 time phase was designated as the end-inspiration (EI) time phase and T_4 time phase as the end-expiration (EE) time phase.

Internal gross target volume and center displacement for esophageal cancer

Sketching of gross tumor volume for primary esophageal tumor (GTV): When sketching target region, take thickness of esophagus wall more than or equal to 5 mm or diameter of esophagus more than or equal to 10 mm when closed as determination standard for primary lesion of esophageal cancer, the same physician of Radiotherapy Dept. will respectively complete sketching of target region on 10 respiratory time phases with 4D-CT for each patient and 3D-CT image to get corresponding GTV. GTV of primary tumor does not include mediastinal lymph nodes.

Definition and acquisition of internal gross target volume (IGTV) of esophageal cancer: (1) Make GTV obtained from sketching of ten respiratory time phases of 4D-CT fused to get $IGTV_{4D}$ (i.e., ideal ITV, taking it as reference target region); (2) Make GTV at end-inspiration (EI, T_0) and end-expiration (EE, T_4) time phase fused-to get $IGTV_{4D'}$. Some scholars proposed that $IGTV_{4D'}$ can be used for replacing $IGTV_{4D}$ to reduce sketching workload of target region [1]; (3) Extend outwards GTV of 3D-CT as per the upper limit of 95% confidence interval of the movement scope of esophageal cancer target region at different segments measured by 4D-CT imaging to $IGTV_{3D}$. (4) Take T_0 time phase image of 4D-CT as reference, capture fusion image of $IGTV_{4D}$ and $IGTV_{4D'}$ and 3D-CT image for registration for standard point of digital image captured through same scanning condition for T_0 time phase based on T_0 time phase image; obtain three-dimensional space coordination for $IGTV_{4D}$, $IGTV_{4D'}$ and $IGTV_{3D}$ and volume under same coordinate system and record through Pinnacle 3 (Version 9.2) treatment planning system.

IGTV center displacement capture: Obtain 3D space position coordinate for $IGTV_{4D}$, $IGTV_{4D'}$ and $IGTV_{3D}$ center point by calculation of Pinnacle 3 treatment planning system and obtain displacements at selected interphase at left-right, anterior-posterior and superior-inferior directions and record them.

Table 1. Comparison in center displacement for different respiratory time phases for each group of esophageal cancer IGTV under the pattern of 4D-CT

Groups and displacement direction	Mean ± SD (cm)	95% (CI*) upper limit	χ^2 value	*P* value
Group A (n = 4)				
Left-right direction	0.16 ± 0.03	0.20	2.0	0.368
Anterior-posterior direction	0.18 ± 0.01	0.20		
Superior-inferior direction	0.24 ± 0.08	0.36		
Group B (n = 7)				
Left-right direction	0.27 ± 0.06	0.32	10.57	0.005
Anterior-posterior direction	0.26 ± 0.08	0.34		
Superior-inferior direction	0.51 ± 0.12	0.62		
Group C (n = 11)				
Left-right direction	0.30 ± 0.12	0.44	17.07	0.001
Anterior-posterior direction	0.31 ± 0.10	0.37		
Superior-inferior direction	0.85 ± 0.26	1.02		

Notes: A group is about patients with upper thoracic segment esophageal cancer, B group is about patients with mid-thoracic segment esophageal cancer, C group is about patients with middle-lower thoracic segment esophageal cancer. *CI refers to confidence interval.

Similarity coefficient and overlap index

The similarity coefficient and overlap index was evaluated according to previously published method [2], $IGTV_{4D}$ was used as "gold standard" to calculate dice similarity coefficient (DSC) and overlap index (OI) for $IGTV_{4D}$ and $IGTV_{4D'}$ and $IGTV_{3D}$.

DSC is defined as the ratio of two times of intersection for A target region and B target region to the sum of A target region and B target region, which can be seen in formula (1); take 0 to 1 for DSC, mainly reflecting consistency of two target regions.

$$DSC = \frac{2(A \cap B)}{A + B} \qquad \text{Formula (1)}$$

OI is defined as the ratio of intersection for A target region and B target region to A target region, which can be seen in formula (2). OI mainly reflects inclusion degree for two target regions, and value is adopted as 0 to 1. In formula (2), A target region is standard volume (i.e., $IGTV_{4D}$).

$$OI = \frac{A \cap B}{A} \qquad \text{Formula (2)}$$

Statistical analysis

SPSS 17.0 statistical software was adopted for statistical analysis. Data was expressed in mean ± standard deviation ($\overline{X}$ ± SD). Comparison of displacement difference among target region centers for ten respiratory time phases of primary esophageal tumor at different segments of 4D-CT was tested by Friedman test. Comparison of volumes for $IGTV_{4D}$, $IGTV_{4D'}$ and $IGTV_{3D}$ was compared by Greenhouse-Geisser method of variance analysis repeating measurement of data and Bonferroni method of pairwise comparisons. Comparison of volume for $IGTV_{4D}$, $IGTV_{4D'}$ and $IGTV_{3D}$ for target region of primary esophageal tumor at each segment was compared by t test. Finally, statistical analysis was made on DSC and OI for $IGTV_{4D}$ and $IGTV_{4D'}$ and $IGTV_{3D}$ for further comparing difference among target regions for three kinds of tumors. When $P < 0.05$, it showed difference of statistical significance.

Results

Displacement for target region center of primary tumor

In 10 respiratory time phases of 4D-CT, Friedman test results for maximum displacement for target region center of primary tumor in esophageal cancer in different segment for 22 patients at left-right, anterior-posterior and superior-inferior directions could be seen in **Table 1**. Difference of displacement in target region center of esophagus primary tumor in mid-thoracic segment, middle-lower at left-right, anterior-posterior and superior-inferior directions had statistical significance. Through further analysis, it could be seen that displacement difference between mid-thoracic segment and middle-lower esophageal cancer target region center at superior-inferior, left-right and anterior-posterior directions had statistical significance, but displacement difference between left-right directions and anterior-posterior directions had no statistic difference.

Comparison of volume and displacement for target region of primary tumor in esophageal cancer

Mean volume value of $IGTV_{4D}$, $IGTV_{4D'}$ and $IGTV_{3D}$ for 22 patients with esophageal cancer could

Table 2. Volume of target region of primary tumor in esophageal cancer for each group

Method \ Groups	Mean ± SD (cm^3)		
	$IGTV_{4D}$	$IGTV_{4D'}$	$IGTV_{3D}$
Group A (n = 4)	48.39 ± 4.62	41.39 ± 2.64	51.71 ± 3.72
Group B (n = 7)	30.19 ± 6.91	25.82 ± 6.86	35.54 ± 8.64
Group C (n = 11)	55.98 ± 31.27	45.85 ± 26.58	68.5 ± 36.22

Notes: Group A is about patients with upper thoracic segment esophageal cancer, Group B is about patients with mid-thoracic segment esophageal cancer, Group C is about patients with middle-lower thoracic segment esophageal cancer.

Table 3. Comparison in target region volume between $IGTV_{4D}$, $IGTV_{4D'}$ and $IGTV_{3D}$ of esophageal cancer

Volume (I)	Volume (J)	Mean value difference (I-J)	*P* value	95% CI	
				Lower bound	Upper bound
$IGTV_{4D}$	$IGTV_{4D'}$	7.203	0.001	4.716	9.691
	$IGTV_{3D}$	-7.141	0.001	-10.495	-3.787
$IGTV_{3D}$	$IGTV_{4D'}$	14.344	0.001	9.503	19.185

be seen in **Table 2**. Volume difference for $IGTV_{4D}$, $IGTV_{4D'}$ and $IGTV_{3D}$ had statistics difference (G-G method, $P = 0.001$), description of paired comparison results (**Table 3**) by Bonferroni method: $IGTV_{3D} > IGTV_{4D} > IGTV_{4D'}$.

Additionally, volume of $IGTV_{4D}$, $IGTV_{4D'}$ and $IGTV_{3D}$ was further paired for t test to study difference between $IGTV_{4D}$, $IGTV_{3D}$ and $IGTV_{4D'}$ at different esophageal segments: relation of $IGTV_{3D} > IGTV_{4D} > IGTV_{4D'}$ existed for volumes of target region of primary tumor in esophageal cancer at upper thoracic segment, mid-thoracic segment, middle-lower thoracic segment.

DSC and OI of esophageal cancer $IGTV_{4D}$ and $IGTV_{4D'}$ to $IGTV_{4D}$ and $IGTV_{3D}$

As shown in **Table 4**: mean DSC value for $IGTV_{4D}$ and $IGTV_{3D}$ of esophageal cancer for whole group was 0.83 ± 0.04, less than average DSC value of $IGTV_{4D}$ and $IGTV_{4D'}$ of 0.90 ± 0.04; while mean OI value of the former was 0.91 ± 0.05, larger than 0.82 ± 0.06 of the latter. Therefore, relative to $IGTV_{4D}$, target region $IGTV_{3D}$ sketched using 3D-CT image outspreading would cause that surrounding normal tissue was exposed to unnecessary irradiation (9-24%); target region $IGTV_{4D'}$ fused from two time phases including end-inspiration and end-expiration would cause failed irradiation for tumor target region (10-34%).

Discussion

According to report of 2015 Annual Report of Tumor in China [3], incidence of esophageal cancer ranked the fifth among malignant tumors in China, mortality rate ranked the fourth. Radiotherapy was very important in the treatment of moderate advanced esophageal cancer. Compared with conventional radiotherapy technology, IMRT can lower radiation volume [4], and further improve local control rate of esophageal cancer and other malignant tumors when lowering irradiation dose to surrounding vital organs. The radical radiation therapy, pre- and postoperative adjuvant radiotherapy and others for esophageal cancer are helpful for improving therapeutic effect for moderate and advanced patients and improving quality of life [5-8]. At present, one of main problems faced by implementing precise radiotherapy of esophageal cancer is accurately defining internal target region in IMRT plan. Esophagus is located deeply in post-mediastinum; peristalsis of esophagus itself, respiratory movement and cardiac great vessels beating and others are main influential factors contributing to displacement of fractionated internal target region for radiotherapy [9].

At present, formulation of radiotherapy plan mostly adopts 3D-CT simulation technology to collect CT images clinically, but the technology cannot accurately reflect the rule of human organs changing and moving with respiratory movement, so clinically, IGTV is mainly formed through outspreading based on GTV according to size of positioning error. This method may cause failed irradiation on tumor, and also may easily cause that excessive adjacent normal tissues are exposed to unnecessary irradiation. In recent years, emerging 4D-CT simulation technology fuses time information into CT imaging, which can not only more authentically reflect size, morphology and position information of tumor, but also can more accurately reflect movement scope and spatial position change rule of thoracic and abdominal tumors. It has been found that 4D-CT can accurately evaluate the situation of lung tumor moving with respira-

Table 4. DSC and OI value for esophageal cancer $IGTV_{4D}$ and $IGTV_{3D}$ and $IGTV_{4D}$ and $IGTV_{4D'}$ for each group

Groups	Items	DSC-A	OI-A	DSC-B	OI-B
Upper thoracic segment (n = 4)	Median	0.86	0.89	0.92	0.85
	Scope	0.80-0.91	0.82-0.96	0.90-0.95	0.83-0.90
	Mean value	0.86 ± 0.05	0.89 ± 0.07	0.92 ± 0.02	0.86 ± 0.03
Mid-thoracic segment (n = 7)	Median	0.85	0.95	0.92	0.85
	Scope	0.78-0.87	0.79-0.98	0.83-0.94	0.75-0.89
	Mean value	0.84 ± 0.04	0.91 ± 0.07	0.89 ± 0.04	0.83 ± 0.05
Lower thoracic segment (n = 11)	Median	0.82	0.93	0.89	0.80
	Scope	0.76-0.88	0.87-0.99	0.79-0.94	0.66-0.88
	Mean value	0.82 ± 0.04	0.93 ± 0.03	0.89 ± 0.04	0.80 ± 0.07
All (n = 22)	Median	0.84	0.93	0.91	0.83
	Scope	0.76-0.91	0.79-0.99	0.79-0.95	0.66-0.90
	Mean value	0.83 ± 0.04	0.91 ± 0.05	0.90 ± 0.04	0.82 ± 0.06

DSC-A is dice similarity coefficient for $IGTV_{4D}$ and $IGTV_{3D}$; OI-A is overlap index for $IGTV_{4D}$ and $IGTV_{3D}$; DSC-B is dice similarity coefficient for $IGTV_{4D}$ and $IGTV_{4D'}$; OI-B is overlap index for $IGTV_{4D}$ and $IGTV_{4D'}$.

tory movement [10]. Target region defined using data of 4D-CT and formulated plan can improve irradiation dose in target region and can reduce irradiation dose on surrounding normal tissue at the same time.

In the study, displacement for target region center for primary tumor for ten respiratory time phases for 4D-CT is not consistent with esophageal cancer at different segments, movement range of upper thoracic segment is smaller than that of target region of primary esophageal tumor at mid-thoracic segment or middle-lower thoracic segment, which may be related to the anatomical position. The result is consistent with relative reports. Studies showed that, movement range of esophagus at lower thoracic segment was bigger than that of esophagus at mid-thoracic segment [11, 12], which was dominant at superior-inferior direction [12]. A previous research has used 4D-CT to conduct correlation analysis on target region displacement in three-dimensional and surrounding adjacent tissues and organs for 17 patients with middle-lower thoracic segment esophageal cancer [13]. Results showed that under quiet breathing state, correlation existed between displacement at 3D direction for target region and displacement of right lung and heart, and correlation existed between change on GTV of primary esophageal tumor during respiratory cycle and change on volume of both lungs. This showed that respiratory movement was one of main influential factors for esophageal cancer displacement.

Displacement and morphological change of target region are the main factors determining esophageal cancer GTV. Movement at 3D direction of target region of primary esophageal tumor belongs to a kind of irregular movement. Therefore, when expanding outward, expansion of target region at left-right, anterior-posterior and superior-inferior directions also shall be uneven outspreading. Ideal esophageal IGTV shall be as below: sketching GTV respectively on image of 10 respiratory time phases for 4D-CT, before fusing them into $IGTV_{4D}$ [1, 14]; but its disadvantages is that doctor's workload of sketching target region is ten times of that of 3D-CT. Therefore, some scholars proposed that $IGTV_{3D}$ can be obtained in movement scope of target region caused by physiological movement and other respiratory movement, positioning error, etc. by combining literature reports and empirical value outspreading based on 3D-CT image.

Analysis on and integration with similarity and crossing relation between position center point of target region, volume and appearance information can show features of spatial position for different target regions, which has great clinical significance. The study showed that inclusion degree of $IGTV_{3D}$ for $IGTV_{4D}$ was better, which can better cover $IGTV_{4D}$, but it's not highly consistent with $IGTV_{4D}$ target region, i.e., if $IGTV_{3D}$ is used to replace $IGTV_{4D}$ for radiation therapy, at most 24% normal tissue is exposed to unnecessary irradiation. In radiotherapy for lung cancer, Li Fengxiang' research group [15] used

3D-CT, 4D-CT and cone-beam CT to conduct comparative study on position and volume of internal target region for lung cancer, and found that IGTV evenly outspreading based on 3D-CT could be better included ITV originated from cone-beam CT, but volume was much greater than the latter, and this would cause that more surrounding normal lung tissues were exposed to unnecessary irradiation. This reflects advantages of 4D-CT simulation.

Two groups of images at EI and EE time phases theoretically represented two extreme positions for respiratory movement of two lungs. Therefore, some scholars proposed that, IGTV$_{4D'}$ fused from GTVs for EI and EE of 4D-CT can be used to replace IGTV$_{4D}$, to reduce workload of sketching target region [1]. However, in the study using 4D-CT for lung tumor [16], IGTV obtained by the method was not suitable for radiotherapy of lung tumor, and cannot comprehensively cover information of respiratory intermediate state. Furthermore, nonidentity between thoracic respiration and abdominal respiration and features of pneodynamics and others had caused the phenomenon of lagging tumor movement [17]. From this, displacement of tumor target region on EI and EE time phase image was not really extreme position for tumor to move. [18] 4D-CT has been used to conduct comparative study on volume of primary tumor for 13 esophageal cancer patients, and results showed that simple use of target region through fusion of two time phases including end-inspiration and end-expiration could not include all movement displacement information of primary tumor. Result of the study showed that consistency of IGTV$_{4D'}$ and IGTV$_{4D}$ target region was higher, but the inclusion degree for IGTV$_{4D}$ was worse, especially for median OI at middle-lower segment was only 0.8, which might be related to great activity of esophagus at middle-lower segment. If IGTV$_{4D'}$ is adopted to replace IGTV$_{4D}$ for radiotherapy, at most 34% tumor volume will not be exposed to irradiation, which increased probability of tumor relapsing and locally failing to control.

Conclusion

In sketch of target region of primary tumor for esophageal cancer intensity modulated radiation therapy, 4D-CT simulation technology is superior to 3D-CT simulation technology, and 4D-CT simulation technology will be helpful for individualized precise radiotherapy for esophageal cancer. Furthermore, low-dose 4D-CT imaging technology method needs to be further explored.

Disclosure of conflict of interest

None.

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