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Analysis of influence factors of cone beam CT calibration in prostate cancer

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Abstract: Objective To deeply explore influence of three objective factors-rectal muscle tension, intra-abdominal pressure and bone in pelvic on cone beam CT calibration data of prostate cancer before radiotherapy and obtain the main factors affecting prostate target movement, so as to provide reference for optimizing radiotherapy plan design and improving image guidance accuracy. Methods Ten eligible patients with prostate cancer were screened according to the inclusion-exclusion criteria for test and scanned twice a week before random treatment by using cone beam CT to obtain prostate target calibration data. After the scanning, the influence of rectal muscle tension was quantified by using shear wave elastography, the influence of intra-abdominal pressure was indirectly quantified by air bag pressure gauge which measured the intra-bladder pressure, and the influence of bone in pelvic was quantified by using root mean square. The relationships between the three factors and cone beam CT calibration data were analyzed by using regression analysis. Results The cone beam CT calibration result was 0.513 mm±0.072 mm, 1.369 mm±0.162 mm, 1.335 mm±0.271 mm on left-right, anterior-posterior and superior-inferior direction respectively for all the patients. Young's modulus value was 8.965 kpa±1.391 kpa, 10.211 kpa±1.544 kpa, 3.926 kpa±0.693 kpa on three directions respectively, intra-abdominal pressure (without direction) was 4.844 mmhg±1.347 mmhg (1mmhg = 133.3 Pa) and root mean square was 0.020 mm±0.011 mm, 0.069 mm±0.049 mm, 0.062 mm±0.029 mm on three directions respectively. Rectal muscle tension (R = 0.895) and intra-abdominal pressure (R = 0.523) on anterior-posterior direction were statistically correlated with the cone beam CT calibration data, and intra-abdominal pressure (R = 0.717) on superior-inferior direction was statistically correlated. Conclusions Rectal muscle tension on anterior-posterior direction and intra-abdominal pressure on superior-inferior direction were the main factors that caused prostate cancer target movement. The results were of great significance to optimize radiotherapy plan design and improve image guidance accuracy and provided methodological guidance for future target displacement reduction.

Keywords: Prostate cancer; Cone beam CT; Shear wave elastography; Intra-abdominal pressure; Root mean square; correlation

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0 Introduction

Cone beam CT (CBCT) has been widely used in image-guided radiotherapy [1-3]. Especially before volume modulated arc therapy (VMAT) for prostate cancer, the positioning can be adjusted according to the calibration data of target displacement during treatment, so as to improve the treatment accuracy.

There are many factors that affect the calibration of CBCT. In addition to subjective factors such as human and mechanical factors that have little and controllable influence, there may still be many unstable objective factors, such as rectal muscle tension, intra-abdominal pressure (IAP) and pelvic bones.

Among the rectal muscles, the rectum involuntary muscle mainly includes the internal rectal sphincter with continuous involuntary weak contraction and relaxation and the rectum longitudinal muscle with downward joint longitudinal muscle to assist the sphincter movement [4]. The movement of the involuntary muscle may be one of the factors causing the target displacement; Intraperitoneal pressure represented by intravesical pressure may affect target displacement; Although the bone ring composed of sacrum, coccyx and bilateral hips does not directly affect the displacement of the target area, it may indirectly cause displacement error by affecting the CBCT calibration data. Therefore, it is particularly important to explore and quantify the impact of three objective factors on CBCT calibration, and there is no relevant literature and research in China.

This test records CBCT calibration and three objective factor data, and uses regression analysis to study the relationship between them. The main purposes are: (1) Explore the main influencing factors in each direction; (2) The target displacement was predicted by the quantitative value of objective factors and regression equation, so as to optimize the design of radiotherapy plan; (3) Take scientific and feasible measures to weaken the influence of objective factors, so as to reduce the CBCT calibration error in the future, that is, to reduce the target displacement in the treatment.

1 Data and methods

1.1 Research object

Ten postoperative prostate cancer patients admitted to the Radiotherapy Department of the First Affiliated Hospital of Hebei North University from September 2018 to September 2019 were screened (median age 65.6 years, 52~73 years).

Inclusion criteria: a. Inserting urinary catheter after operation; b. Body index mass (BIM) is between 18~25, and there is no peritoneal effusion; c. Other functions of genitourinary system and other physiological and biochemical indexes except prostate specific antigen were normal.

Exclusion criteria: a. Prostatic hypertrophy and severe calcification; b. Rectal polyps, hemorrhoids (not conducive to marker implantation); c. Other diseases unfavorable to radiotherapy.

Gleason score [5]: 1 case with ≤ 6 points, 1 case with 7 points and 8 cases with ≥ 8 points. All patients voluntarily signed informed consent. This trial was reviewed and approved by the medical ethics committee of the First Affiliated Hospital of Hebei North University.

1.2 Equipment and methods

1.2.1 Test equipment

(1) MEDA synergy accelerator (MEDA, Sweden) equipped with CBCT to perform VMAT; (2) Visicoil helical linear gold marker (IBA, Belgium); (3) Aixplore color Doppler ultrasound diagnostic instrument (supersonic, France); (4) VBM airbag pressure gauge (VBM, Germany).

1.2.2 Image guided radiotherapy

(1) Marker implantation. Before treatment, three markers were implanted into different layers of prostate cancer target area by transrectal ultrasound-guided surgery and fine needle aspiration [6-8], with a three-dimensional space of ≥ 15 mm.

(2) Schedule CT scans. The pelvic scan was performed in supine position. Except for the prostate area of 0.5 mm, the thickness of other areas was 3 mm to ensure the resolution of the target area. It is required to forbid diet, completely empty bladder and rectum, and the previous treatment status is the same [9].

(3) Plan design. Using the Monaco planning system, the imaging findings of prostate (seminal vesicle) and encapsulated tumor area were defined as gross tumor volume (GTV); Imaging findings showed that pelvic enlarged lymph nodes were defined as pelvic positive lymph node GTV (gtv_nd); Prostate (seminal vesicle gland as appropriate) and associated lymph node drainage area were defined as clinical target volume (CTV); the planning target volume (PTV) is defined as the outward expansion of 0.8 cm (0.5 cm behind the CTV boundary to protect the rectum). PTV prescription is 67.5 Gy /25 times, 5 times a week. The treatment mode is 1f2a (one field and two arcs) in Pareto mode, and the maximum number of sub fields per arc is 100.

(4) CBCT scan. After the start of formal treatment, each patient received a total of 10 CBCT scans before treatment (twice a week), and the calibration data were used to adjust the positioning. Record and calculate the average value of 10 CBCT calibration displacements in each direction for each patient.

1.2.3 Rectal muscle tone measurement

At the same time of treatment on the accelerator machine tool, each patient received 10 times of B-ultrasound measurement before treatment (twice a week). Using 2~10 mhz high frequency linear array probe to measure the young's modulus of rectal muscle in three directions: at 2 cm directly below the left/right femoral head and at 15~25 cm depth depending on the patient's fat thickness, measure the rectal muscle echo and muscle fiber movement in the left and right directions; At 2 cm below pubic symphysis and 5~10 cm deep depending on the fat thickness of the patient, the echo and muscle fiber course in the front and back directions were measured; At the anus, set a depth of 2~3 cm to measure the echo in the direction of head and foot and the course of muscle fibers. Select shear wave elastography (SWE) mode and set 13 mm × 13 mm square selection box at the measuring muscle. After the color in the square selection box is filled evenly for about 10 s, freeze the image, turn on the Q-box function, set the measurement area to a circular selection box with a diameter of 5 mm, and automatically calculate the young's modulus of muscle tissue in the selection box [10-12]. Record and calculate the average value of Young's modulus calculated by 10 swe in each direction for each patient.

1.2.4 IAP measurement

At the same time of treatment on the accelerator machine tool, each patient received 10 times of IAP measurement before treatment (twice a week). For the patients who have inserted Freund's catheter, the nurse uses the balloon manometer to measure the bladder pressure according to the IAP standard measurement method and process, and obtains the IAP through the conversion formula [13-14]. Record and calculate the average value of 10 times IAP for each patient.

1.2.5 Pelvic bone impact calculation

Three markers were used to calibrate the displacement of CBCT and bernchou et al. [15] developed an algorithm to quantify the impact of pelvic bones, that is, root mean square (RMS) of calculation error. RMS refers to the influence and error caused by the radiation attenuation caused by pelvic bones calculated by CBCT projection images on the calibration accuracy of the center points of the three markers. For example, the RMS algorithm in the left and right directions of the center points of the three markers in the ith CBCT projection image is shown in formula (1).

$$\mathrm{RMS}_{\mathrm{LR},i} = \sqrt{\frac{1}{n}\sum_{j=1}^{n}\left(x_{i,j} - \frac{1}{n}\sum_{j=1}^{n}x_{i,j}\right)} \quad (1)$$

Where: i is the number of CBCT projection image. A total of 660 projection images were obtained by CBCT scanning in this test, that is, i is any integer number from 1 to 660; j is the number of the marker, j is any number in 1, 2 and 3; n is the number of markers, i.e. $n = 3$; $X_{i,j}$ are the CBCT calibration displacement in the left and right directions of the marker numbered j on the i CBCT projection image. Calculate the RMS mean value of 660 projected images after each CBCT calibration and the total mean value after 10 CBCT calibrations in each direction of each patient: $\mathrm{RMS}_{\text{pelvic bones}}$.

1.2.6 Statistical treatment

SPSS 19.0 software was used for processing.

A. Measurement data conforming to normal distribution: The mean value of CBCT calibration displacement and the mean value of three factors (IAP without direction) of 10 patients in three directions are expressed as mean ± standard deviation ($x \pm s$).

B. Pearson method was used to analyze the relationship between three single factors such as CBCT calibration displacement and rectal muscle tension in three directions, and the correlation coefficient r was calculated (the absolute value of R between 0~0.1 was no correlation, 0.1~0.4 was weak correlation, 0.4~0.6 was moderate correlation, 0.6~1 was strong correlation). Bilateral test was used for significance test (α= 0.05), with p<0.05 as the result, it has statistical significance.

C. The factors with statistical significance in the results of correlation analysis were included in the regression analysis.

Table 1 Description results of measurement data

	Direction		
	About	Around	Head and foot
CBCT calibration displacement /mm	0.513±0.072	1.369±0.162	1.335±0.271

Young's modulus value /kPa	8.965±1.391	10.211±1.544	3.626±0.693
IAP/mmhg	4.844±1.347	4.844±1.347	4.844±1.347
$RMS_{pelvic\ bones}$/mm	0.020±0.01	0.069±0.049	0.052±0.029

2 Results and analysis

2.1 Measurement data description

The results of measurement data description are shown in Table 1, in which IAP values of all patients are within the normal range: (5±2.9) mmhg(1 mmhg = 133.3 Pa).

2.2 Correlation analysis

The results of single factor correlation analysis between CBCT calibration displacement and rectal muscle tension, IAP and pelvic bone in three directions are shown in Table 2. In the left and right directions, the CBCT calibration displacement was weakly or not correlated with the three single factors, and the results were not statistically significant; In the anterior and posterior directions, CBCT calibration displacement was strongly correlated with rectal muscle tension and moderately correlated with IAP. The results were statistically significant, but not with pelvic bones; In the head foot direction, the CBCT calibration displacement was moderately correlated with IAP, and the results were statistically significant. The results were weakly or not correlated with rectal muscle tension and pelvic bones, and the results were not statistically significant.

Table 2 Results of correlation analysis

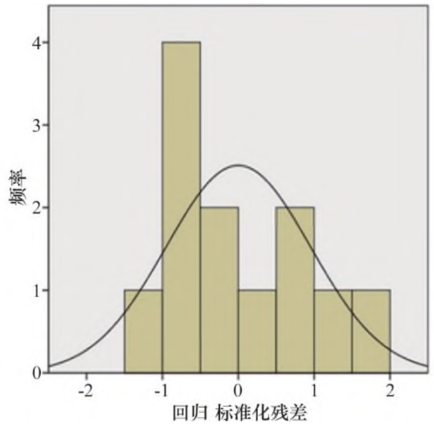
Direction	Factor	No value	P value
About	Rectal muscle tone	0.144	0.741
	IAP	0. 105	0. 542
	Pelvic skeleton	0.074	0. 879
Around	Rectal muscle tone	0. 878	0. 000
	IAP	0. 523	0. 039
	Pelvic skeleton	0.119	0. 704
Head and foot	Rectal muscle tone	0.211	0. 228
	IAP	0. 717	0. 009
	Pelvic skeleton	0.058	0. 466

2.3 Regression analysis

The relationship between rectal muscle tension (X_1), IAP (X_2) and CBCT calibration displacement (Y) was analyzed by multiple linear regression.

(1) The determination coefficient of model fitting: the complex correlation coefficient r is 0.704, and the determination coefficient R^2 is 0.495. Combined with the relatively symmetrical standardized residual histogram on the left and right sides (Figure 1) and the standardized residual P-P diagram with scattered points basically close to the slash (Figure 2), it is considered that the model fitting is good.

(2) Table 3 shows the regression coefficient values and their standard errors and P values in the final model. It can be seen that rectal muscle tension has a greater impact on CBCT calibration displacement than IAP. According to the influencing factors and partial regression coefficients in the table, the regression equation is obtained: $Y = 85.266-14.782X_1-8.559X_2$.

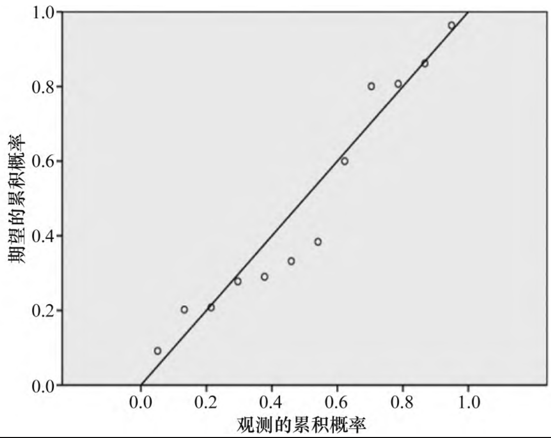


Frequency
Regression standardized residual

Figure 1 Standardized residual histogram on anterior-posterior direction

Univariate linear regression analysis was performed on the relationship between IAP (x) and CBCT calibration displacement (y) in the head foot direction.

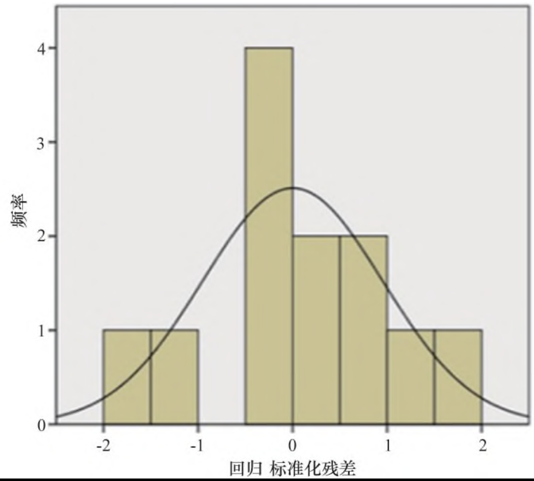
(1) Determination coefficient of model fitting: R2 is 0.837, and the error of standard estimation is 0.128. Combined with the relatively symmetrical standardized residual histogram on the left and right sides (Figure 3) and the standardized residual P-P diagram with scattered points basically close to the slash (Figure 4), it is considered that the model fits well.



Expected cumulative probability
Cumulative probability of observation

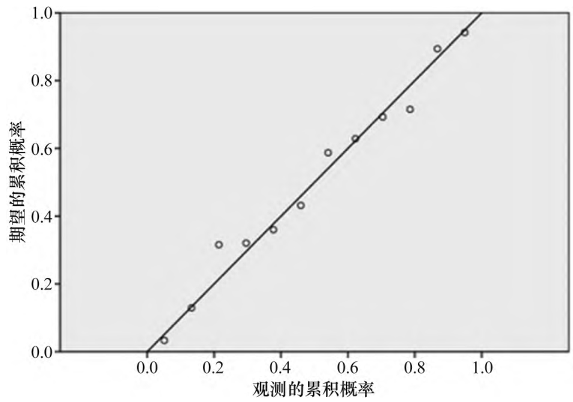
Figure 2 Standardized residual P-P diagram on anterior-posterior direction

(2) Table 3 shows the value of regression coefficient, its standard error and P value in the model finally used. According to the influencing factors and regression coefficient in the table, the regression equation is obtained: Y =-22.466+17.974X.



Frequency
Regression standardized residual

Figure 3 Standardized residual histogram on superior-inferior direction



Expected cumulative probability
Cumulative probability of observation

Figure 4 Standardized residual P-P diagram on superior-inferior direction

Table 3 Regression coefficient

Direction	Project	*B*	SE	*t* value	*P* value
Around	Constant	85.266	3.129	79.278	0.000
	Rectal muscle	14.782	3.697	5.492	0.039

	tone				
	IAP	8.559	2.508	–3.889	0.024
Head and foot	Constant	–22.466	1.192	–16.295	0.017
	IAP	17.974	1.708	–2.520	0.022

Note: B -partial regression coefficient or regression coefficient; SE -standard error.

3 Discussion

In rectum muscle, the tension in the left, right, front and back directions mainly comes from the involuntary movement of the internal sphincter. From the correlation analysis results, it can be seen that the tension in the left and right directions of the internal sphincter has little effect on the left and right displacement of the prostate cancer target area, but the tension in the front and back directions is the main cause of the front and back displacement of the target area; the tension in the head foot direction mainly comes from the involuntary movement of the rectum longitudinal muscle. From the correlation analysis results, it can be seen that the tension in the head foot direction of the rectum longitudinal muscle has little effect on the displacement in the head foot direction of the prostate cancer target area. Therefore, how to limit the movement of internal dilator muscle is of great significance to reduce the displacement of prostate cancer target.

The internal sphincter of rectum belongs to smooth muscle and has extensibility. This muscle fully relaxes to ensure sufficient expansion of the anal canal, but the internal sphincter is usually in an involuntary continuous contraction state, so as to close the anus and avoid fecal leakage, which is the most important function of this muscle [4].

Internal sphincter tension is easily enhanced by external transient stimulation, such as gastrointestinal flatulence and thin stool stimulating the ampulla of rectum, which can cause reflex muscle tension enhancement. More importantly, the internal sphincter has the inherent characteristics of the circular muscle of the digestive tract, that is, it is prone to spasm. The muscle spasm can be caused by general persistent harmful stimulation, such as drug enema, anal crypt inflammation, hemorrhoids, dysentery, proctitis and sympathetic hyperstimulation. Persistent spasm will change the muscle structure, leading to permanent contracture, namely internal sphincter achalasia. Because of the tension change caused by the transient or continuous stimulation of the internal dilator muscle, it will have a significant impact on the anterior and posterior displacement of the prostate cancer target. Therefore, prostate cancer patients should try to avoid the above-mentioned stimulation before radiotherapy. If there is an old history of prostate cancer, patients should be cured before radiotherapy. At the same time, patients should be given appropriate treatment adaptability training to reduce psychological pressure, so as to prevent excessive sympathetic tension, so as to reduce the impact on the front and back displacement of the target area of prostate cancer.

Normal IAP is mainly maintained by gravity, organ morphology and uniform pressure [16]. The results of correlation analysis showed that IAP changes in patients with prostate cancer were the main cause of head foot displacement in the target area and the secondary cause of fore-and-aft displacement.

In terms of gravity, if the content of the abdominal cavity decreases, its mass will significantly increase the pressure of the lower abdomen (such as bladder and prostate). In the radiotherapy of prostate cancer patients, BMI not only has a great impact on image-guided calibration, but also the abdominal fat gravity of obese patients with Abnormal BMI value with changes in body position or abdominal contents can increase the IAP of the lower abdomen by 3 times. In addition, in the process of positioning and fixing patients, the uncertain tension of thermoplastics mold and the clamping force will affect the position of abdominal fat. The above effects will cause significant displacement of prostate target. In terms of organ deformation, the upper abdominal organ deformation caused by respiratory movement, that is, diaphragmatic flattening movement, has a certain impact on IAP and will increase the lower abdominal pressure. In terms of uniform pressure, the abdominal cavity contains enough liquid that can move freely and maintain and conduct normal IAP. In case of peritoneal effusion, the liquid will uniformly transfer the pressure and increase the lower abdominal pressure. In conclusion, before radiotherapy, patients with prostate cancer should control BMI, breathe quietly and remove peritoneal effusion.

Patients with Abnormal BMI and peritoneal effusion were excluded from this trial. Therefore, the change of IAP was mainly affected by respiratory movement. Therefore, during the treatment of prostate cancer patients, we must ensure calm breathing and avoid strenuous chest exercise. If patients with lung and heart diseases that lead to abnormal breathing should be cured as much as possible before radiotherapy. At the same time, we should carry out appropriate respiratory adaptability training for patients, so as to reduce the impact on the head and foot of the prostate cancer target area and the front and back displacement.

To sum up, in the left and right directions: The influence of three factors on CBCT calibration data of prostate cancer was weak and irregular. However, the results of several similar random tests show that [1-3], the CBCT calibration data in the left and right directions are small, so the value can be directly used as empirical data after multiple averages.

In the fore-and-aft direction: the main influencing factor is the change of rectal muscle tension caused by the fore-and-aft movement of the internal rectum dilator muscle, and the secondary influencing factor is the change of IAP caused by the fore-and-aft gravity of abdominal fat. Using the regression equation, CBCT calibration data can be accurately predicted by independent variables.

In the head foot direction: the main influencing factor is the change of IAP caused by organ deformation caused by respiratory movement. Using the regression equation, CBCT calibration data can be accurately predicted by independent variables.

In a word, the target displacement of prostate cancer can be predicted by quantifying the influencing factors and regression equations in the fore-and-aft and head foot directions, so as to optimize the radiotherapy plan design and reduce the image-guided calibration error; At the same time, necessary and feasible measures can be taken to reduce the displacement of the target area in the future.

In addition, the research ideas provided by this test may have reference value for other tumor targets [17], such as the displacement of rectal cancer targets.

4 Conclusion

Rectal muscle tension in the anterior posterior direction and IAP in the head foot direction are the main factors causing the target displacement of prostate cancer. The results are of great significance for optimizing the radiotherapy plan design and improving the image guidance accuracy, and provide methodological guidance for reducing the target displacement in the future.

The results obtained from the trial are of great clinical value and open up new research ideas, but the trial still has certain limitations: (1) The sample size is small, so the number of samples needs to be expanded; (2) The swe measurement method needs to be improved. The measurement in three directions passes through different tissues, which will cause measurement errors. Direct transanal color Doppler ultrasound may effectively solve this problem; (3) IAP is not divided into directions, only the total IAP value is measured, and the IAP value in each direction is not quantified. It is still necessary to study the partial pressure measurement method in each direction.

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