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Clinical and experimental observation of the length of time of respiratory phase: a preliminary study

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Abstract. – OBJECTIVE: Our goal was to observe the duration of inhaling and exhaling as well as the inhalation to exhalation conversion in patients with lung cancer and experimental dogs.

MATERIALS AND METHODS: We recorded lung and tumor respiratory motion with X-ray camera, in five patients with lung cancer as well as in five experimental dogs. We made random observation of breathing cycle inhalation duration, exhalation duration, and inhalation to exhalation conversion within each lung cancer patients and within each of the five animals.

RESULTS: Respiratory inhalation duration of each dog and human > exhalation duration > exhale to inhale conversion length > inhalation to exhalation conversion length. During the four breathing cycles, the total respiratory duration differs, and the length of the same breathing phase is inconsistent.

CONCLUSIONS: The measurement of early stage breathing duration cannot be representative of breathing duration of the late stage. Radiation treatment planning system based on the pre-computed tomography scanning on the basis of early stage, there will be some radiation dose errors.

Key Words:
Respiratory Phase, Radiation therapy, Radiation dose.

Introduction

The conformal radiotherapy and IMRT (Intensity-Modulated Radiation Therapy) is a new technology in radiation oncology that delivers radiation more to the tumor while sparing the surrounding normal tissues. It can make tumor target area more accurate, in reducing the radioactive damage on normal tissue and it can improve the curative effect through an increased target dose[1,2]. The location of the tumor can change because of respiratory motion and, thereby, the remote local control rate of tumor is reduced. Previous research has been focused on target space position and normal tissue profile changes (because of tissue breathing exercise), but no studies have been reported on the differences and their impact on the accuracy of tumor. In view of this situation, we have conducted a preliminary study.

Materials and Methods

Animals

We conducted our study on five healthy dogs, weighing from 10 to 15 kg, male or female. Each dog was anaesthetized by intraperitoneal injection (IP) of 10% chloral hydrate (4.5 ml/kg). After a resting period, the dogs were fixed on the board in a supine position. We used simulated location X-ray unit (Nuclear Power Institute of China, Potential brand, HMD-IA model) to do the consecutive perspective of the whole chest. The central simulator point was selected on the board surface and on the back of the dog. The perspective and video lasted for a total of 3 to 5 minutes. The video was then transferred to a computer using the universal timer software V1.1.0 to observe and record the respiratory cycle. After having chosen the top right diaphragm as the observation point, we collected five respiratory cycles for each dog by random sampling and recorded the duration of (1) inhalation, (2) exhalation, (3) inhalation to exhalation conversion and, (4) exhalation to inhalation conversion.

Patients

Amongst the patients with inferior lung cancer who were receiving radiotherapy in our department from February to March 2012, we chose a total of five cases (3 male and two female) with

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good lung function. We obtained informed consent from each patient and asked them to breathe normally and calmly in order to observe and record by video. The simulator's central point was located at the lung tumor to observe the respiratory motion of the tumor.

Data Processing

We recorded the length of each time phase, and we compared the differences. Using the SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA), we performed one-way ANOVA. We considered $p < 0.05$ has statistically significant.

Results

Animal Model Results

The results obtained in the dogs are shown in Tables I and II. From Table I, we observed in each of the dogs, the duration of inhalation to respiration, respiration to inhalation conversion, inhalation to respiration conversion. The difference in inhalation and exhalation time were compared individually using variance analysis, and we obtained $F = 5.151$, $p < 0.05$. For inhalation time versus inhalation to exhalation conversion time, our variance analysis was $F = 49.954$, $p < 0.05$. Comparing inhalation time to inhalation conversion time, we obtained $F = 4.365$, $p < 0.05$ which was statistically significant.

Patient Results

The results obtained in patients are shown in Tables III and IV. As showed in Table III, each patient showed the same pattern, i.e. inhalation duration; respiration duration; respiration to inhalation conversion duration; inhalation to respiration conversion duration. When comparing the differences between inhalation and respiration duration, we obtained $F = 4.202$, $p < 0.05$. When comparing the differences between the respiration duration and respiration to inhalation conversion duration, we obtained $F = 52.138$, $p < 0.05$. When comparing the differences between the inhalation duration and inhalation to respiration conversion duration parameters, we obtained $F = 5.231$, $p < 0.05$, and p was considered statistically significant.

Table I. Results obtained in five dogs.

Dogs		Inhalation duration (seconds)	Inhalation to resp. duration (seconds)	Respiration duration (seconds)	Resp. to insp. duration (seconds)	Total breathing duration (seconds)
No. 1	1	1.20	0.73	1.45	0.86	4.24
	2	1.39	0.65	1.18	0.78	4.00
	3	1.43	0.5	1.05	0.84	3.82
	4	1.38	0.72	1.23	0.76	4.09
	5	1.45	0.69	1.15	0.83	4.12
No. 2	1	1.33	0.62	1.29	0.91	4.15
	2	1.35	0.70	1.22	0.88	4.15
	3	1.39	0.65	1.20	0.87	4.11
	4	1.41	0.63	1.19	0.89	4.12
	5	1.29	0.68	1.15	0.95	4.07
No. 3	1	1.38	0.69	1.23	0.92	4.22
	2	1.22	0.64	1.18	0.78	3.82
	3	1.35	0.67	1.17	0.79	3.98
	4	1.45	0.62	1.25	0.83	4.15
	5	1.29	0.71	1.16	0.85	4.01
No. 4	1	1.35	0.64	1.20	0.81	4.00
	2	1.06	0.72	0.98	0.84	3.60
	3	1.41	0.83	1.31	0.82	4.37
	4	1.39	0.67	1.26	0.80	4.12
	5	1.42	0.66	1.19	0.75	4.02
No. 5	1	1.39	0.71	1.13	0.91	4.14
	2	1.43	0.67	1.16	0.88	4.14
	3	1.45	0.69	1.05	0.96	4.15
	4	1.40	0.69	1.24	1.01	4.34
	5	1.48	0.66	1.15	1.20	4.49

Table II. Respiratory measurement results in dogs.

Average inhalation duration 1.36 ± 0.09s	Insp. to resp.[1] average duration 0.67 ± 0.05s	Average respiration duration 1.19 ± 0.09	Resp. to insp.[2] average duration 0.86 ± 0.09s
Maximum inhalation duration 1.48s	Max insp. to resp. duration 0.83s	Maximum respiration duration 1.45s	Max resp. to insp. duration 1.2s
Minimum inhalation duration 1.06s	Min insp. to resp. duration 0.5s	Minimum respiration duration 0.98s	Min resp. to insp. duration 0.75s

Note: [1]insp. to resp. indicates inhalation to respiration conversion duration; [2]resp. to insp. Indicates respiration to inhalation conversion duration

In both patients and dogs, the results showed the same pattern, i.e. each inhalation duration; respiration duration; respiration to inhalation conversion duration; inhalation to respiration conversion duration. The differences between each parameter was always statistically significant with a $p < 0.05$. Comparing every breathing time to the total breathing duration changes, we observed a range of differences from 0.03 to 0.50 seconds and the breathing phase differs from 0.01 to 0.40 seconds. We also noticed that after several regular breathings, a longer deep inhalation and slow respiration would follow. Briefly speaking, the respiratory motion is not a simple mechanical repetition because the total duration and each phase are changing. Unfortunately, we did not conduct long term observation to be able to determine whether these changes are consistent with normal distribution. Moreover, the external radiotherapy plan did not take the stay or move time of the therapeutic targets in various locations into consideration. With one or two respiratory phase of target position to develop a plan of treatment, the time span to the influence of ra-

Table III. Results obtained in 5 patients with lung cancer.

Patients		Inhalation duration (seconds)	Inhalation to resp. duration (seconds)	Respiration duration (seconds)	Resp. to inhalation duration (seconds)	Total breathing duration (seconds)
No. 1	1	1.22	0.83	1.34	0.82	4.22
	2	1.29	0.75	1.08	0.79	3.91
	3	1.45	0.65	1.15	0.82	4.07
	4	1.38	0.72	1.23	0.76	4.09
	5	1.47	0.66	1.25	0.84	4.22
No. 2	1	1.44	0.68	1.3	0.89	4.31
	2	1.36	0.72	1.32	0.9	4.3
	3	1.38	0.67	1.22	0.8	4.07
	4	1.4	0.71	1.28	0.82	4.21
	5	1.36	0.67	1.18	0.92	4.13
No. 3	1	1.42	0.66	1.21	0.84	4.13
	2	1.22	0.69	1.18	0.78	3.87
	3	1.45	0.73	1.27	0.81	4.26
	4	1.43	0.69	1.28	0.89	4.29
	5	1.33	0.64	1.29	0.91	4.17
No. 4	1	1.26	0.65	1.32	0.83	4.06
	2	1.15	0.64	0.99	0.87	3.65
	3	1.4	0.72	1.32	0.85	4.29
	4	1.38	0.77	1.16	0.78	4.09
	5	1.4	0.76	1.29	0.86	4.31
No. 5	1	1.29	0.73	1.25	0.79	4.06
	2	1.37	0.71	1.26	0.76	4.1
	3	1.46	0.79	1.14	0.87	4.26
	4	1.34	0.74	1.21	1.05	4.34
	5	1.38	0.67	1.19	1.12	4.36

Table IV. Respiratory measurement results in patients with lung cancer.

Average inhalation duration 1.39 ± 0.07s	Insp. to resp.[1] average duration 0.68 ± 0.06	Average respiration duration 1.15 ± 0.05	Resp. to inhalation[2] average duration 0.89 ± 0.09s
Maximum inhalation duration	Max inhalation. to resp. duration	Maximum respiration duration	Max resp. to inhalation duration
1.45s	0.83s	1.35s	0.91s
Minimum inhalation duration	Min inhalation to resp. duration	Minimum respiration duration	Min resp. to inhalation duration
1.15s	0.64s	0.99s	0.76s

Note: [1]inhalation to resp. indicates inhalation to respiration conversion duration; [2]resp. to inhalation. Indicates respiration to inhalation conversion duration.

diation dose is obvious. Take the conformal radiotherapy at a time in accordance with 120 seconds to calculate, the dose rate in accordance with 200cGy/min, the actual beaming time is about 60 seconds, and the affected range of each radiation dose is about 0.062-6.25cGy. In the intensity-modulated radiation, due to the changes in the sub-wild position, the actual impact requires precise calculations.

Discussion

The conformal radiotherapy and IMRT require treatment target accuracy in delineation and a high repeatability. With the continuous technological improvement and the development of image-guided radiotherapy, the impact of positioning errors on 3D conformal radiotherapy and IMRT to treat lung cancer has been reduced. However, the impact of the chest tumor fine radiotherapy dose accuracy highlights another important factor which includes respiratory motion, which has been plagued by cancer radiotherapy workers[3]. For breast cancer, the target areas and normal tissue contour changes because of breathing exercise, which can lead to actual absorbed dose differences with curative effect[4]. As a result, this affects the judgments of the physician response to normal tissue reactions.

Radiotherapy experts and researchers have recognized the impact on the radiotherapy accuracy of the target displacement due to the respiratory motion. Tumors can move and even change in shape with the respiratory motion. Previous studies considered the impact on radiotherapy of the target and normal tissue contour changes brought by the tumor displacement due to the respiratory motion. Since now, the methods to resolve the impact of the respiratory motion on the lung cancer radiotherapy include individualized ITV (Internal Target Volume) delineation, the breathing control techniques, the respiratory gating radiotherapy and the real-time tracking radiotherapy, etc. The main methods of individualized ITV delineation include: (1) slow scanning (slow spiral CT scan), CBCT (Cone-beam computed tomography) and PET (Positron Emission Tomography) which are often adopted as the scan method and (2) gated CT scan and rapid 4D CT (Four Dimension Computed Tomography) which are often used as the quick scanning method. These resolving methods apply to the lung cancer with a small range of motion. Concerning those with greater range of motion, the radiation dose enhancement is not conductive because of the defined target volume boundaries due to the motion artifacts, and a larger ITV volume. The breathing control techniques include ABC (Active Breathing Control) technology[5,6] and DIBH (Deep Inhalation Breath-Hold) technology[7,8] as representatives. The technology is applicable for patients with good lung function after training, which limits its wide application in patients with lung cancer. In the radiotherapy procedures, respiratory gating technology (RG) uses a method to monitor patients' breathings and triggers beam irradiation in particular breathing phase. This technology adopts various respiratory motion labeling methods to realize the real-time monitoring of the target area, and then selects a specific breathing phase to undertake the radiotherapy. Based on the relationship between the label and patients, RG radiotherapy can be divided into two forms (i.e., internal and external RG). Real-time tracking technology during radiotherapy in patients with correlation wiring harness or real-time position adjustment, to ensure that the beam

and target area have the same spatial location. None of the above techniques have taken into account the unevenness of the respiratory motion speed, the changes in duration of each breathing movement and each breathing phase. So far, there are no reports on the four respiratory phases' rules, differences, or the impact on the accuracy of tumors radiotherapy.

The point of this study was to observe the relationship between various respiratory motional organs in space and time. For example, suppose that the respiratory cycle duration is consistent with that of a certain organ or target within the body and that the length of time of the breathing phases is consistent with each other, and the space displacement during each breath is also repeated. In virtue of this, we established the mathematical relationship of the respiratory motion *in vivo* and *in vitro*. During patient observation, we confirmed that the respiratory motion is not an accurate repetition, and that the correspondence between *in vivo* and *in vitro* respiratory motion were not obvious. Considering the possible inaccuracy in distance and time measurement, we tried to adjust the spatial accuracy of the simulator to 1 mm, but we were not able to place the organ *in vivo* and *in vitro* on the center point of the simulator. Changing our way of thinking, we decided to re-adjust the time precision to 0.01 seconds without calculating the spatial accuracy, and found that it was very easy to realize.

In a free-breathing state, the lung tumor displacement is more significant in the vertical direction than that in other directions. Furthermore, it was observed that the tumor displacement in lower lung was more significant than that in upper and middle lung[8]. In order to facilitate our observation, we focused on the test results. Our findings indicate that animal respiratory regulations are similar to human. During every breath, the inhalation duration; respiration duration; respiration to inhalation conversion duration; inhalation to respiration conversion duration. There are differences between each breathing time and between the same respiratory phases of each breathing time. In fact, after several regular breathings, there is always an irregular breathing with duration change, therefore bringing the displacement change. Even if the displacement difference is not taken into account, the time difference can explain the external radiation dose difference.

When using a multi-slice CT for positioning, the entire breathing duration is not necessary. The obtained CT image is an image of several respiratory phases, and the lineated target area can correspond to the phase and spatial displacement at that time. Since the starting time of the CT scan is random, neither positioning technicians nor doctors can determine the breathing phase during the scan or the extroverting CTV to PTV. Considering this will surely bring a larger PTV.

Since the duration of the respiration to inhalation conversion is relatively longer, and the inhalation is slightly slower than the respiration, we can certainly start the quick positioning CT scan at the end of the respiration, and complete the image positioning scanning with the multi-slice CT in one second. By doing this, when extroverting CTV to PTV, we only need to consider the spatial and time differences of the respiratory motion. The treatment plan based on deep inhalation superior to free-breathing has confirmed our point of view[9]. It is believed that the treatment plan based on the deep inhalation breath-hold is better, since it is more favorable to patients with left breast cancer[10].

Considering the time and location differences of every respiratory motion, based on the respiratory motion before radiotherapy, the positioning CT scan that constructs the so-called 4-position Ct and 4-D radiotherapy plan will consider only the displacement differences[11], but unable to take into consideration the duration and position changes of each breathing phase in the respiratory motion during the radiotherapy. In fact, most of the real-time verification devices are testing the body surface breathing, but not monitoring the target area breathing. It can be speculated that, the impact on the displacement and time of the breathing phase will bring again the uncertainty due to the inconsistency of displacement and time with the in vivo target while doing the monitoring on body surface breathing. We believe that neither the surface breathing signal, nor other indirect breathing signal in non-treated area is reliable.

The ABC may be a more reliable method[12]. The ABC based on moderate deep inhalation is similar to our CT positioning plan at the end of breathing[13]. The cone-beam CT guidance and MLC tracking technology can contribute to the implementation of our ideas as well[14,15], but we still have to consider the measuring error brought by the delay time when the breathing signal triggers to start the machine, or we can appropriately take in advance the triggering signal. The real-

time 4D radiotherapy still has many technical and equipment problems to resolve[16]. Considering the change of the breathing time length, it is a relatively feasible technology to control patients' respiratory motion. At present, the adopted clinical methods such as the active breath-hold by patients, respiratory gated-control and active breath-control are relatively realistic approaches[17].

The appearance of 4D-CT technology cannot only represent tumor' real shape, but also can reflect tumor's motion regulation, design patient's individual radiotherapy plan according to the characteristics of the target motion, increase the accuracy of radiotherapy, and improve tumor treatment effect[18]. However, the 4-D plan cannot solve the time changes between one and another breathing cycle. The real-time tracking of patient's respiratory motion to increase the accuracy of positioning and treatment can maximize the irradiation dose of the tumor tissue, corresponding with the radiation oncology principles[19]. Patient pulmonary function differences together with the individual difference before and after breathing phase variation need to be studied in depth. The breathing phase change and its impact on radiotherapy needs further study.

Conclusions

The earlier measured breathing duration cannot be completely represented by the later measured breathing duration. The radiotherapy plan systems based on earlier CT scan technology will have a certain error of radiation dose.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Jiang J, Wang Q, Xiao Z. Efficacy of three-dimensional conformal radiotherapy for 132 patients with oesophageal carcinoma. Chinese J Radiation Oncol 2009; 18: 47-51.
2) Yang H, Liu W, Liao X, Xiang L, Zhang Y. Clinical study on conventional radiotherapy and three-dimensional conformal radiotherapy for oesophageal cancer. China Cancer 2010; 19: 143-147.
3) Li B. Management of respiration motion in precise and accurate radiotherapy of lung cancer. Chinese J Cancer Prevent Treat 2008; 15: 1601-1604.
4) Liu Q, McDermott P, Burmeister J. Effect of respiratory motion on the delivery of breast radiotherapy using SMLC intensity modulation. Med Phys 2007; 34: 347-351.
5) Wong JW, Sharpe MB, Jaffray DA, Kini VR, Robertson JM, Stromberg JS, Martinez AA. The use of active breathing control (ABC) to reduce margin for breathing motion. Int J Radiat Oncol Biol Phys 1999; 44: 911-919.
6) Yan J, Yu JM, Li BS, Fu Z, Wang XT, Zhou T. [Application of active breathing control system to precise radiotherapy for non-small cell lung cancer]. Ai Zheng 2006; 25: 1311-1314.
7) Hanley J, Debois MM, Mah D, Mageras GS, Raben A, Rosenzweig K, Mychalczak B, Schwartz LH, Gloeggler PJ, Lutz W, Ling CC, Leibel SA, Fuks Z, Kutcher GJ. Deep inhalation breath-hold technique for lung tumors: the potential value of target immobilization and reduced lung density in dose escalation. Int J Radiat Oncol Biol Phys 1999; 45: 603-611.
8) Langen KM, Jones DT. Organ motion and its management. Int J Radiat Oncol Biol Phys 2001; 50: 265-278.
9) Marchand V, Zefkili S, Desrousseaux J, Simon L, Dauphinot C, Giraud P. Dosimetric comparison of free-breathing and deep inhalation breath-hold radiotherapy for lung cancer. Strahlenther Onkol 2012; 188: 582-589.
10) Shim JG, Kim JK, Park W, Seo JM, Hong CS, Song KW, Lim CH, Jung HR, Kim CH. Dose-volume analysis of lung and heart according to respiration in breast cancer patients treated with breast conserving surgery. J Breast Cancer 2012; 15: 105-110.
11) Moorees J, Bezak E. Four dimensional CT imaging: a review of current technologies and modalities. Australas Phys Eng Sci Med 2012; 35: 9-23.
12) Gong GZ, Yin Y, Xing LG, Guo YJ, Liu T, Chen J, Lu J, Ma C, Sun T, Bai T, Zhang G, Wang R. RapidArc combined with the active breathing coordinator provides an effective and accurate approach for the radiotherapy of hepatocellular carcinoma. Strahlenther Onkol 2012; 188: 262-268.
13) Sager O, Beyzadeoglu M, Dincoglan F, Oysul K, Kahya YE, Gamsiz H, Uysal B, Demiral S, Dirican B, Surenkok S. Evaluation of active breathing control-moderate deep inhalation breath-hold in definitive non-small cell lung cancer radiotherapy. Neoplasma 2012; 59: 333-340.
14) Zhong R, Wang J, Jiang X, He Y, Zhang H, Chen N, Bai S, Xu F. Hypofraction radiotherapy of liver tumor using cone beam computed tomography guidance combined with active breath control by long breath-holding. Radiother Oncol 2012; 104: 379-385.

15) Davies GA, Poludniowski G, Webb S. MLC tracking for Elekta VMAT: a modelling study. Phys Med Biol 2011; 56: 7541-7554.

16) Shirato H, Onimaru R, Ishikawa M, Kaneko J, Takeshima T, Mochizuki K, Shimizu S, Umegaki K. Real-time 4-D radiotherapy for lung cancer. Cancer Sci 2012; 103: 1-6.

17) Chang J, Mageras GS, Yorke E, De Arruda F, Sillanpaa J, Rosenzweig KE, Hertanto A, Pham H, Seppi E, Pevsner A, Ling CC, Amols H. Observation of interfractional variations in lung tumor position using respiratory gated and ungated megavoltage cone-beam computed tomography. Int J Radiat Oncol Biol Phys 2007; 67: 1548-1558.

18) Zhang S, Zhou L, Xu H, Chen G, Lin S, Wang S. New advance on 4D-CT reconstruction and its application. Chinese J Med Phys 2009; 26: 1046-1050.

19) Burnett SS, Sixel KE, Cheung PC, Hoisak JD. A study of tumor motion management in the conformal radiotherapy of lung cancer. Radiother Oncol 2008; 86: 77-85.