

Evaluation of Malignant Lung Tumor Motion Comparing to Fix Point during Different Respiratory Phases on Four-Dimensional Computed Tomography

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ABSTRACT

Introduction: One of the most important problems in different radiotherapy methods in lung cancer tumors is the movement of the lung during the respiratory cycle and the subsequent motion of the tumor. Changing the shape and displacement of the tumor during radiotherapy increases the radiation to the surrounding normal tissues and decreases the radiation dose to the tumor tissue. The displacement of the lung and the path of the tumor can be traced.

Methods: In an analytical study, the amount of lung tumor displacement during different phases of breathing, using four-dimensional (4D) computed tomography (CT) (4D CT) scan images in order to reduce the radiation dose to normal tissues and the maximum possible dose radiation to the target tissue, in radiotherapy treatment of lung tumors, was checked during the respiratory cycle. Also, the amount of movement of the diaphragm and tumoral tissues under the diaphragm during the respiratory cycle was estimated. Biomechanical models were used to predict the position of different parts of the lung at the end of the exhalation phase using images related to the end of the inspiratory phase.

Results: In examining the displacement of three markers in each patient, the average of displacement was 4.4 mm in the right-left (RL) direction, 6.15 mm in the anterior-posterior (AP) direction and 8.6 mm in the superior-inferior (SI) direction ($P=0.001$), while the average of overall displacement was 11.25 mm. Also, the difference in overall displacement was the lowest in the SI direction (2.6 mm) compared to 6.8 and 5.1 mm in the RL and AP directions, respectively.

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Conclusion: *By using 4D CT scan imaging it is possible to measure the exact position of the tumor in order to predict its movement pattern during the respiratory cycle, which is based on the examination and modeling of the change in position and motion of different parts of the lung and it is done using information related to respiratory dynamics.*

Keywords: lung cancer, radiotherapy, tumor movement.

INTRODUCTION

According to the pathology and progression of some cancerous tumors, radiotherapy is considered one of the main treatment methods. The aim of radiotherapy is to introduce a high dose of radio waves into the tumor and prevent its growth by the process of cell destruction, while preserving the natural tissues around the lesion from receiving radiation. Therefore, in radiation therapy, increasing the dose reached to the tumor and reducing the absorbed dose by the surrounding healthy tissues is particularly important (1). The accuracy of radiation therapy in the chest area is subject to many factors, of which movement is the most important one. Movement can be caused by the heart rate, nearby muscles and bones, the digestive system and, most importantly, by breathing, which can cause transmission and moving, rotating and changing the shape of the members, with changes having specific and regular size, direction, phase and linear paths (2). From another point of view, breathing is a dynamic and physiological process and can have daily changes and different patterns for each person.

These cases make it especially important to find the location of tumors and their position in relation to surrounding healthy organs and sensitive tissues in order to increase the accuracy of radiation therapy (1). The concept of radiation therapy with the help of images expresses the different methods of imaging in this field. Image guided radiation therapy (IGRT) can be defined as the addition of imaging technology to new radiation therapy devices, a technology that has had a significant growth rate in the past years. One of the most important applications of IGRT is radiation therapy in lung cancer, a process that plays an important role in increasing the tumor dose, reducing the number of steps required for treatment, increasing the quality of dose applica-

tion, reducing toxicity and adjusting the dose based on anatomical and physiological changes (3). The data obtained from three-dimensional (3D), 4D and magnetic resonance imaging (MRI) and CT scans can be used to track lung tumors. The tracking can be done using the markers determined in the total imaging data (4).

In the past, radiotherapy treatments were performed with the assumption that the tumor was fixed in the patient's body during treatment periods, although it was long later realized that such an assumption was incorrect; however, there was no technology to stop or track this movement (5). One of the methods was to create a reliable border in order to consider the movement of the tumor by increasing the target volume, which was followed by an increase in the radiation field (6). Imaging, design and application of treatment during the last two decades have improved a lot with technology and the possibility of 4D modeling of the desired organ or tissue from the patient's body has been provided, which includes three spatial dimensions and the fourth dimension which is time.

The time factor is considered because, in living and active organs, circular movements and, for example, the filling of abdominal organs are happening continuously – hence, the effect of different types of motions on patients' images and the application of the effective dose will be transitory and variable. These changes depend on the proximity of the moving target and the organs at risk, the type of motion and its range, or the ability to reproduce the movement in the shortest possible time and from day to day (for example, in bowel cancer, the movement of the digestive system during the course of radiation therapy causes the motion of the target tissue as well as the nearby organs at risk, which causes disruption and stoppage of treatment). In such cases, the movements will be non-intermittent and unpredictable, and consequently, their modeling will be difficult (7, 8).

On the other hand, lung motions caused by breathing are semi-intermittent movements and their changes over the course of treatment will be predictable; therefore, in the dynamic adaptations, tumor can be considered a moving target with a specific and periodic motion path (1). In 3D imaging, the main rule of imaging is based on the stability of the object. Therefore, the imaging of moving organs such as chest and abdominal organs will lead to the creation of artifacts in the reconstructed images, which will lead to the creation of an incorrect location of the object, darkness and distortion of the boundaries of the object, incorrect shape and size in the image, while clarity and differentiation will decrease and noise will increase in the image (9). Methods designed to reduce artifacts were first considered for cardiac motions and then applied to movements caused by breathing in the chest, although the main purpose of these methods was to reduce artifacts in order to create images for diagnostic applications, and not treatment (10).

Over the past years, the expansion of the use of 4D imaging such as CT scan has made it possible to measure the motion of organs inside the chest and lung tumors during breathing. The ability to measure the exact position of the tumor in order to predict its movement pattern during the respiratory cycle requires accurate information about the dynamics of breathing and its effect on the distribution of radiation on the tumor and surrounding tissues in radiotherapy (11, 12). Given the limited number of studies on the use of 4D CT scan imaging, in order to investigate the pattern of changes in lung tumor position and motion during the respiratory cycle in Iran, the present study was aimed to use 4D CT scan imaging in radiation therapy for pulmonary tumors. □

MATERIAL AND METHOD

In the present descriptive/analytical study, data from 4D CT images of seven patients with non-small cell lung cancer (NSCLC) were collected, which included 10 different phases of a complete respiratory cycle. Images were arranged based on the distance from the apex of the lung to the diaphragm (Figure 1).

The preparation of images and their arrangement in the order of different respiratory phases was considered the first step in the biomechanical

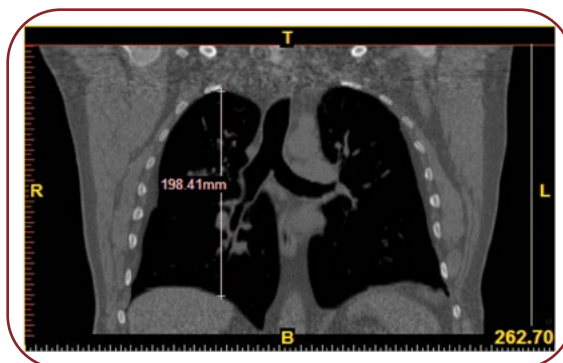


FIGURE 1. Determining the respiratory phase by measuring the distance from the apex of the lung to the diaphragm at the end of the exhalation phase

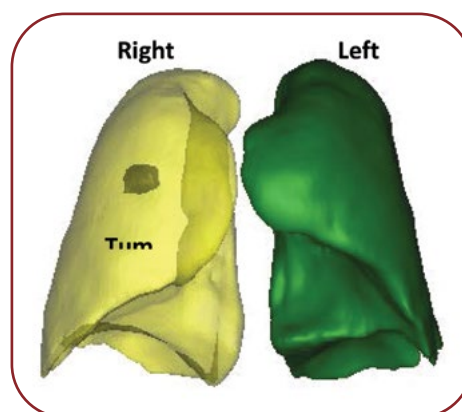


FIGURE 2. Left lung, right lung and the tumor inside it from the front view, with the right lung being shown semi-transparent to see the tumor (patient 1 in early phase)

cal modeling of lung motion. The relationship between lung volume and tumor volume as well as how they moved were also investigated. The next step was to separate the lung tissue and tumor from other parts of the chest. In the present study, the end phase of inhalation was considered as the initial phase of the lung and the end of exhalation phase was considered as the final phase. In each phase, the left and right lung and tumor tissues were isolated using Mimics 10.01 software (Figure 2). In each slice, according to the different Hounsfield unit (HU) values, different tissues of the lung tissue were separated from other tissues.

Since most of the lung volume is made up of air and the lung parenchyma is made of a low-density tissue, the HU value was chosen between two specific values and close to each other.

Given the existence of a clear border between the lung tissue from the chest muscles and the diaphragm, it is easy to separate them from each other. But in the part where the heart is located and in the navel of the lung where the main bronchi enter, due to HU proximity, these bronchi and the heart and the surrounding tissues of the lung with the main bronchi inside the lung, which is considered a part of the lung in the presented model, cannot be automatically isolated like its other parts. Therefore, these parts had to be manually added to the lung mask in each slice of the image. In order to determine the markers inside the lung, the parts with HU and higher density were used (Figure 3). Points such as the branching place of the main vessels or the branching place of the air tubes were good options for the purpose because they were well visible on the 4D CT images. These points are markers that can be used to check the displacement of different parts of the lung, and the difference in coordinates of these points at the end of the inhalation and exhalation phases is used to check the biomechanical model. The hilum or navel of the lung is the place where the main bronchi of the main vessels of the lung (red vein and pulmonary vein) as well as the pulmonary nerves enter; it is also the place where the visceral pleura is connected to the parietal pleura. Due to the direct connection of the lung to the trachea, the point remains fixed in all breathing phases and does not move or rotate. In the area of the chest cavity (i.e., the place where the side wall is connected to the diaphragm) there is not much movement in the anterior-posterior (AP)

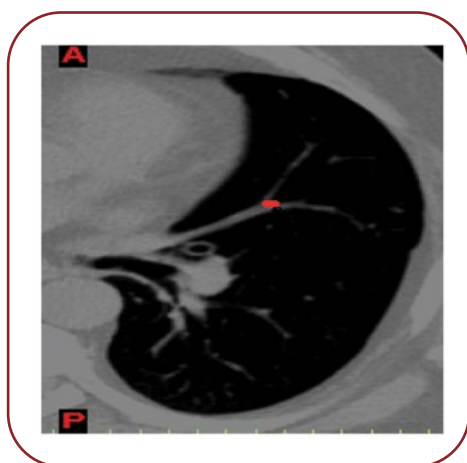


FIGURE 3. Selecting the location of tracheal branching as a marker inside the lung

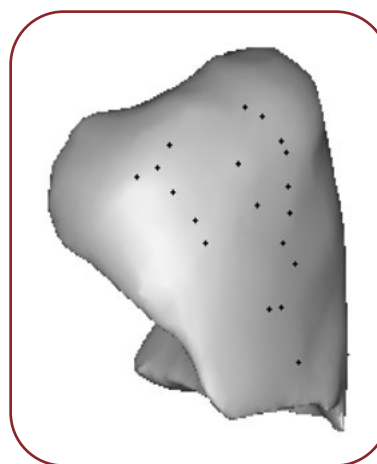


FIGURE 4. Distribution of markers inside the left lung of patient 1

and right-left (RL) directions; therefore, this part can be used as fixed points in the direction of the mentioned motions. Certain points on the vertebrae of the spine in the neck and chest are considered fixed points and no other rotation during the respiratory cycle.

The number of markers for each patient was determined by separating the right and left lungs and their distance from the lung wall (Figure 4).

In designing the biomechanical model, parts of the lung were considered as border areas. These areas were considered as the parts around the lung that had the least displacement, and the amount of displacement of the lung surface was measured in three directions, including superior-inferior (SI), RL and AP, relative to these areas. These conditions were applied to the right lung in three areas and to the left lung in four areas. Also, the defined pressure on the lung during the breathing process plays a role in providing a predictive model of lung motion. As a result, the forces entering the lung from different sides during the respiratory cycle were considered in the biomechanical modeling. The elastic properties of the lung are also effective in the amount of displacement following the applied force. Therefore, in the present study, the elasticity properties of the patients' lungs were determined based on two parameters: Young's modulus and Poisson's modulus. The parameters of the first four patients were adjusted – based on the model requirements and the values obtained from the surface displacements and markers and forces applied to the lung and the elasticity properties of the lung tissue – in such a way that there was the least difference between the predicted value of the displacement from the end of inspiration

to the end of exhalation by the model and the observed experimental value. The remaining three patients' data at the end of the inspiratory phase were then also given to the model and the amount of displacement at the end of exhalation was predicted. Afterwards, these displacements were compared with the actual observed value. The diagram of the difference in displacement of the markers on the 4D CT images was drawn with the corresponding nodes in the biomechanical modeling of lung motion in three different directions in patients 5, 6 and 7. All results were obtained by adjusting the parameters for each patient separately.

Statistical analysis

In our research, Mimics software was used to view images and find points and other parameters related to the lung and tumor. Data analysis was done with SPSS-19 software at 95% confidence level and with One way ANOVA test. $\square$

RESULTS

Data related to 4D CT images were collected from seven patients with NSCLC. They included information related to image dimensions and pixel data of all patients and in 10 different phases of a complete respiratory cycle. The images were sorted based on the distance from the apex of the lung to the diaphragm (Table 1).

The number of markers for each patient was determined by separating the right and left lungs and their distance from the lung wall (Table 2).

In order to more accurately investigate the amount of lung displacement during the respira-

TABLE 1. Patients' data related to image and pixel dimensions

Patient	Image dimensions (pixels)	Pixel dimensions (mm)
1	512 × 512 × 141	0.98 × 0.98 × 2
2	512 × 512 × 169	0.98 × 0.98 × 2
3	512 × 512 × 170	0.88 × 0.88 × 2
4	512 × 512 × 187	0.78 × 0.7 × 2
5	512 × 512 × 181	1.17 × 1.1 × 2
6	512 × 512 × 181	1.17 × 1.17 × 2
7	512 × 512 × 111	0.98 × 0.98 × 3

tory cycle, the displacement of markers in three different directions (AP, RL and SI) was investigated (Table 3). For most of the markers, displacement in the SI direction was higher than that in the remaining two directions.

In all patients, the tumor volume was less than one percent of the lung volume (Table 4).

The displacement average of markers in patients' right and left lungs was calculated in three directions (AP, SI and RL) (Figure 5). The left lung of patient 3 did not have a marker due to its non-opening and was not considered in the analysis. The amount of displacement in the right lung was slightly higher than the left lung in all cases, except for patient 6. Displacement in SI direction was greater than that in the remaining two directions and it was positive in all patients, while displacement in AP and RL directions was positive in some patients and negative in others. The amount of displacement depends on the number of markers and the position chosen for them, although we made the effort to use the same number of markers and similar points for all participants; nevertheless, their number was

TABLE 2.

The number, displacement and distance of markers inside the lung to its wall

Patients	Lung	# of landmarks	Total displacement (mm)			Distance to the lung wall (mm)		
			Average (SD)	Max.	Min.	Average (SD)	Max.	Min.
P1	right	19	8.1 (1.7)	12.1	5.5	25.5 (8.1)	43.1	14.1
	left	19	4.7 (2.5)	8.0	2.7	24.0 (6.3)	38.4	14.8
P2	right	18	15.7 (6.6)	28.7	4.1	25.7 (8.1)	39.2	7.7
	left	17	6.6 (3.5)	12.3	1.6	18.4 (7.9)	33.0	3.9
P3	right	16	10.8 (5.6)	24.2	3.1	24.1 (6.1)	33.2	11.8
	left	-	-	-	-	-	-	-
P4	right	17	7.8 (5.3)	21.0	2.3	21.5 (9.1)	43.3	7.2
	left	10	5.9 (3.8)	14.8	2.1	17.5 (5.1)	23.1	7.0
P5	right	13	4.9 (3.2)	12.9	2.0	24.3 (10.6)	38.5	4.4
	left	14	4.7 (2.8)	10.3	2.1	16.5 (6.9)	30.5	6.9
P6	right	14	6.6 (3.8)	12.9	0.8	20.7 (4.1)	25.8	14.5
	left	12	8.9 (3.5)	12.7	1.0	19.6 (4.8)	28.2	11.2
P7	right	10	5.2 (2.4)	9.3	3.2	23.9 (8.2)	39.7	10.7
	left	12	4.1 (2.4)	9.0	3.0	15.8 (5.8)	26.3	5.5

Patients	Marker No	Maximum of total displacement (mm)	Maximum of RL displacement (mm)	Maximum of AP displacement (mm)	Maximum of SI displacement (mm)
P1	1	10.95	3	4	10
	2	9.11	1	4	9
	3	8.25	1	2	8
P2	1	14.32	6	11	12
	2	12.57	8	7	10
	3	14.87	3	5	14
P3	1	20.45	9	9	16
	2	17.69	8	12	12
	3	20.22	11	12	12
P4	1	10	0	6	8
	2	9	2	4	8
	3	8.25	0	3	8
P5	1	8.31	3	7	8
	2	8.31	2	3	8
	3	8.25	2	4	8
P6	1	11.75	7	6	10
	2	8.60	7	6	4
	3	12.08	7	9	4
P7	1	5	3	4	0
	2	7.07	5	5	3
Total	mean	11.25	4.4	6.15	8.6
Sig*			0.001	0.061	

TABLE 3. The amount of lung displacement during the respiratory cycle and displacement of markers in the right-left (RL), anterior-posterior (AP) and superior-inferior (SI) directions

Patient	Tumor position	Tumor volume (mm ³)	V _{tumor} /V _{lung} (%)
P1	RML	7880	0.24
P2	RUL	2145	0.08
P3	RML	2310	0.10
P4	RML	2973	0.14
P5	LLL	1068	0.06
P6	RUL	10880	0.52
P7	LUL	480	0.04

TABLE 4. Characteristics of tumor volume and lobe location in patients' lungs

RML= right middle lobe; RUL=right upper lobe; LLL=left lower lobe.

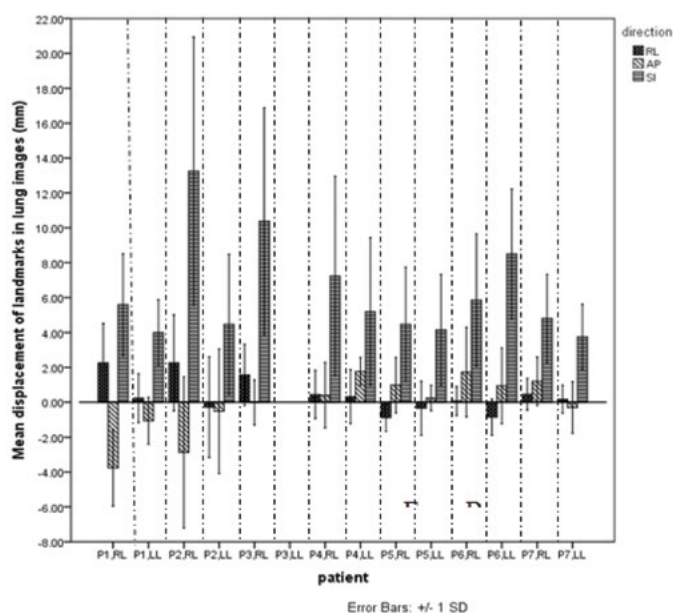


FIGURE 5. Displacement average of markers in the lung images for each patient, separately for the left and right lungs

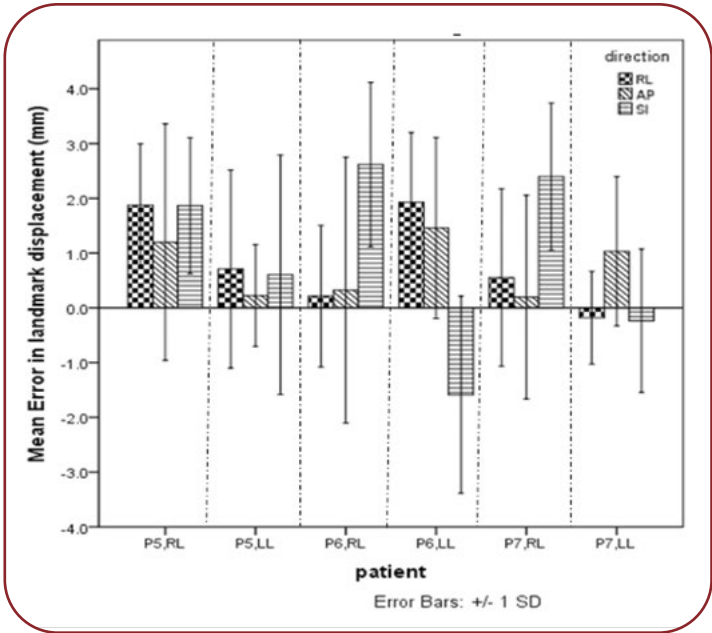


FIGURE 6. Mean difference of displacement of intra-lung markers in computed tomography images and biomechanical model

TABLE 5. The amount of total error and the simulation time of the lungs in patients 5, 6 and 7

Patient	Right (R) and left (L) lungs	Total error (mm)	Time (s)
P5	RL	2.1 (1.1)	110
	LL	- 0.3 (1.7)	119
P6	RL	2.5 (1.9)	121
	LL	- 1.4 (1.4)	123
P7	RL	2.4 (1.0)	83
	LL	- 0.5 (1.3)	71

different in different patients, as shown in Table 3.

The difference in marker displacement on the 4D CT images was calculated with the corresponding nodes in the biomechanical modeling of lung motion in three different directions (Figure 6). The results were obtained using parameters for each patient separately. Negative values indicated more displacement in the image compared to the model, while positive values revealed more displacement in the biomechanical model compared to the original images. Because the lower lip of the right lung of patient 7 did not open, the average values of the averaged forces of the diaphragm were used for it, and the lower lung force was removed.

Table 5 shows the total displacement error value of the patients 5, 6 and 7 along with the simulation time of the left and right lungs. Negative errors show the amount of more displacement of the images compared to the model and

positive error value shows the amount of more displacement predicted by the model compared to the images. □

DISCUSSION

In examining patients’ CT images during different phases, the thoracic vertebrae showed the least amount of displacement during the complete respiratory cycle, as reported in previous studies too (13). The displacement was considered in three directions. For example, some points on the clavicle bone and sternum did not clearly move in the RL direction, while the displacements in the SI and AP directions were significant, so these points cannot be considered as fixed points in order to evaluate the motion of other parts. Tracheal bifurcation in the carina was considered as another fixed point. The amount of tumor and marker displacement was investigated according to the change of their distance in all three directions (SI, AP and RL) from these points.

In examining the displacement of three markers in each patient, the average of displacement was 4.4 mm in the RL direction, 6.15 mm in the AP direction and 8.6 mm in the SI direction; also, when comparing the displacement in the three directions, movement in the SI direction was significantly higher than RL (P=0.001). Compared to the AP direction, there was a clear difference, albeit not statistically significant, from the point of view of clinical examination; also, the difference in overall displacement was the lowest in the SI direction (2.6 mm) compared to 6.8 and 5.1 mm in the RL and AP directions, respectively. Determining the specific points in different places of the lung will represent the particular part in the lung. The points will show the amount and direction of lung motion during the respiratory cycle. The points selected for the purpose had a higher density and more HUs than other parts of the lung, so they were well distinguishable from other parts on the CT images.

The location of the branching of the main bronchi and pulmonary vessels in the navel of the lung were chosen for the purpose. These points were determined for each lung during different breathing phases, with the difference in coordinates of these points at the end of the inhalation and exhalation phases being indicative of the displacement in all three directions. In or-

der to improve the accuracy of our study, the appropriate marker distribution inside the lung and the maximum possible marker for each lung in each person were selected. The right and left lungs of patient 1 had the highest number of markers (19 markers), while the left lung of patient 4 and the right lung of patient 7 had the lowest number of markers (10 markers). The difference in the number of selected markers was due to the difference in patients' CT images, in such a way that the number of points which had sufficient HUs to be selected as markers was greater in the lung of patient 1 than that of the remaining subjects.

In the present study, there were significant variations in the measurement of marker displacement in different patients. Thus, average displacement of markers in all directions had the highest value in the right lung of patient 2 (15.7 mm) and the lowest value in the left lung of patient 7 (1.4 mm). The maximum value of displacement was the highest in the right lung of patient 2 (28 mm) and the lowest in the left lung of patient 1 (8 mm). The minimum value of displacement was the lowest in the right lung of patient 6 and the highest in the right lung of patient 1. The average distance of markers to the lung wall was the highest in the right lung of patient 1 and the lowest in the left lung of patient 7.

Considering the above-described findings, it can be concluded that the displacement of different parts of the lung not only among different people, but also in the left and right lungs of the same person, has significant variations. Therefore, the biomechanical models made from the lung of one person, which are determined based on the amount of displacement of different parts of the lung, the different forces acting on the lung from different directions and the elasticity properties of the lung tissue, cannot be generalized to other people and compared (14). These differences are caused by differences in the lung size of different patients, the volume of inspiratory and expiratory air during each breathing cycle, the volumes of dead air and remaining air at the end of each exhalation, the forces exerted by the respiratory muscles during breathing and the elasticity of the lung tissue (15). The variation in marker displacement in the two lungs of the same person is also caused by the difference in the anatomical structure of the lungs and in the forces exerted on each lung (16).

In order to more accurately investigate the displacement of different parts of the lung during a respiratory cycle, the displacement of markers in different directions (RL, AP and SI) was investigated. In each person, the partial amount of displacement for the three markers located in similar and close places in different patients was selected and their maximum displacements were recorded. In all subjects, except for patient 6, the magnitude of displacement in the SI direction was greater than that of the two remaining directions. The difference is due to the presence of the diaphragm in the lower part of the chest as the main muscle during breathing. The direction of the incoming force is greater in the SI direction compared with RL and AP directions, and the lungs have the greatest freedom of movement in this direction during the respiratory cycle. If there is a tumor, the greatest amount of displacement will be in the SI direction. In all participants to the present study, the tumor volume was less than 1% of the lung volume, which made us expect that such a small percentage would not have an effect on the elasticity of the lung tissue in such a way as to create a significant change in the overall movement of the lungs.

In the four patients examined in the study of Jeason Eom *et al* (9), the average difference between the position of the marker in the images and what was predicted through the biomechanical model was equal to 4.5, 3.8, 3.1 and 2 mm, while in the present study we found that the highest error value was 2.5 mm and the lowest error value 0.3 mm. The above-cited cited authors used 34 CT images in each breathing cycle for each patient to simulate the biomechanical model, while in our study, 10 images were taken during each cycle from each patient. Ehrhardt *et al* (8) predicted the state of the lung from the biomechanical model, just like we did in the present study, and considered the presence of tumor in the lung tissue without affecting its dynamics; in their prediction, the average value of the difference between the predicted value and marker displacement from the end of inhalation to the end of exhalation was 3.3 mm.

In the current study, regardless of the negative value and predicted positive value, the average of displacement was 1.53. In a study of six patients, Zeh Tabian *et al* used a model designed to predict the condition of the lungs of three subjects based on the parameters and data from

images of the remaining three patients. The average value of the predicted displacement and the value observed on the images was 4.5 mm, while in the present study, the maximum displacement was 2.5 and the average value 1.53. In their study, the average duration of predicting lung condition by the model was 89 seconds compared to the present study, which was equal to 104 seconds. Although the prediction time obtained by us was longer compared to the model used by Zeh Tabian *et al*, the error rate was less than half of their study. □

CONCLUSION

Four-dimensional CT scan offers the possibility to measure the exact position of a tumor in order to predict its motion pattern during the respiratory cycle based on examining and modeling the change in position and movement of different parts of the lung by using information about respiratory dynamics. In our study, the amount of tumor tissue movement during different respiratory phases was determined using 4D CT scan images, which increased the efficiency and responsiveness in tracking the tumor

during the respiratory cycle and throughout the course of radiation therapy. Both radiotherapy and reducing damage to adjacent tissues will be effective approaches. The use of this method will also be effective for tumors related to tissues outside the lung that move during the respiratory cycle, such as those occurring in the diaphragm and sub-diaphragm regions. The predictive model of the lung respiratory motion described in the study will be able to predict the end of the exhalation phase in the lung with the end of exhalation phase with a small error compared models used in similar studies. □

Informed consent was obtained from all individual participants included in the study.

Conflicts of interest: none declared.

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