ORIGINAL ARTICLE

Consideration of the target area of radiotherapy for lung cancer with 4DPET

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Abstract

Objective: Through the study of 4-dimensional (4D) positron emission tomography (PET)/computed tomography (CT) for lung tumor, the delineation of the lung tumor target area was analyzed, the accurate target area was received, and the radiation dose of normal tissue was compared.

Methods: The average 4DPET volume, 3DPET volume, average 4DCT volume, and 3DCT volume of 10 tumors were compared. Taking the relative difference between the average 4D volume and the 3D volume as the difference of the volumes, the influence of the tumor size and the range of motion for 4D volume and 3D volume were studied respectively, then the target areas were delineated respectively, and the radiation doses of the normal tissues associated with the respective target areas were compared after the intensity-modulated radiation therapy plan was formulated.

Results: The PET volumes of all tumors were smaller than those of CT, no matter 4D or 3D, from small to large, the volume sizes were 3DPET volume, average 4DPET volume, 3DCT volume and average 4DCT volume. The relative volume difference was related to the respiratory movement and the size of the tumors. The average 4DPET volume was 22.8% larger than the average 3DPET volume, and the volume ratio was 1.23. The volume of the average 4DCT was 15.4% larger than that of the average 3DCT, and the volume ratio was 1.16. The average volume of 4DCT was 59.5% larger than that of 4DPET. When the movement amplitude of the tumor was greater than 3 mm and less than 5 mm, the larger the tumor volume, the larger the volume ratio of the average 4DCT volume to the average 4DPET volume, with the maximum value being 1.54. When the tumor movement amplitude was greater than 5 mm, the ratio was about 1.4. When the volume of conventional 3DCT was larger than 5 cm³, the ratio of the average 4DCT volume to the average 4DPET volume was 1.9. The planning target area (PTA) internal target volume (ITV)3DCT intersected ITV4DCTave and ITV4DPETave, the dose V20 and V5 of normal lung tissue, and the dose V30 of heart were increased accordingly. Of these, the dose of lung and heart of ITV4DPETave was the lowest. The V20 and V5 of lung of ITV4DPETave was about 2% lower than ITV4DCTave.

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Conclusion: To delineate lung tumor targets at various positions, particular attention should be paid to the effect of breathing exercises on large movements and large volumes. The target volume seemed to be overestimated by 4DCT, and the average multi-phased 4DPET volume was more accurate for delineating the target area while reducing the radiation dose of the lung.

KEYWORDS
3D, 4D, lung cancer, positron emission tomography, radiotherapy target, respiratory gated, treatment planning, volume comparison

The target area of radiotherapy is directly affected by the tumor volume, which is usually influenced by the displacement of the target caused by tumor respiratory movement. Especially for lung tumors, the image used in the radiotherapy plan is a static image, but the patient is in the breathing state in the actual treatment process, and the breathing movement will lead to changes in the position of tumors and organs, thus the radiation dose of the target area and organ at risk will be affected. To achieve precision radiotherapy, techniques such as deep inhalation breath-holding, 4-dimensional (4D) computed tomography (CT), etc. are used. In the early literature, it was reported that respiratory gated positron emission tomography (PET)/CT was beneficial for the accurate calculation of lung volume. In recent years, the change of tumor location between 4DPET and 3DPET has been reported, as well as the study of volume change. In addition, 4DCT has been widely used to reduce the artifacts of respiratory movement by continuously capturing the tumor volume in different respiratory periods in a respiratory cycle. The difference between the volume of 4DCT and that of 3DCT has been compared to obtain the accurate delineation of the tumor target.

The purpose of this study was to compare average 4DPET volume, 3DPET volume, average 4DCT volume, and 3DCT volume in different positions of the lung through 4D PET/CT scans and routine 3D PET/CT scans, and thus discover the relationship between tumor motion amplitude, PET volume, and CT volume. The target areas for 3D and 4D were delineated respectively, and the radiation dose of normal tissue related to the target area was compared by radiotherapy planning.

1 | MATERIALS AND METHODS

1.1 | Study subjects

Routine PET/CT scans were obtained for 10 patients who had detected malignant tumors and delayed imaging is a separate collection of the lung after a whole-body PET/CT scan.

1.2 | Acquisition equipment and methods

A GE Discovery VCT PET/CT instrument and the real-time respiratory movement monitoring system (Varian real-time tracking system) were used, and a GE AW4.4 workstation was used for the image processing. The patients were injected with 18F-FDG according to 5.55–7.40 MBq/kg. 4D PET/CT scans were performed after routine 3D PET/CT scans. The scanning range was one bed for all scans with 2 min/bed, and the tumors were placed in the center of the imaging range as far as possible. 4DCT scans were acquired around the tumors with the same scanning conditions. One cycle was divided into six bins based on a percentage of the respiratory cycle (i.e., 0, 20%, 40%, etc.) by GE automatic phase matching software. The PET images of each phase were reconstructed using CT image attenuation correction of the corresponding phase. All PET and CT data were reconstructed with a slice thickness of 3.75 mm.

1.3 | Image processing

3DPET volume, 3DCT volume, six-phased 4DPET volume, and 4DCT volume were measured by Sim Software of the post-processing workstation for the tumor target areas. PET volumes were delineated using two methods, maximum density projection (MIP) and the threshold method. CT volumes were also delineated with the MIP method. Tumor target areas were delineated using a Varian Eclipse station by a radiologist and a nuclear medicine physician, both with 8 years of experience. The PET target areas were contoured with the size of the tumor, the background concentration, and the anatomy of the fused CT. Standardized lung window/level settings (1250 ± 300) were used for the CT data sets.

1.4 | Comparison method

The average six-phased 4DPET volume obtained by the MIP method and the 40% threshold method, 3D PET volume, average six-phased 4DCT volume, and 3DCT volume were compared. We defined %DIFF as the percentage difference of volumes. With the tumor motion amplitude and volume size, the effect of respiratory gated PET/CT on 4D volume and 3D volume was studied. After the target areas were delineated by six-phased 4D PET and 4DCT, the intersection was taken and is shown in Figure 1. The treatment planning was made to compare the radiation dose of the normal tissue associated with each target.
2 | RESULTS

2.1 | Comparison of the average six-phased 4DPET volume, 3DPET volume, average six-phased 4DCT volume and 3DCT volume for each tumor

In this study, 10 tumors were selected, which were located in the upper lung, middle lung, and lower lung (Table 1). The range of motion was 1.7-7.1 mm, with an average of 4.3 mm. The average six-phased 4DPET volume for each tumor was measured by the 40% threshold method and the MIP method. The average 3DPET volume of all tumors was 6.5 cm³, and the average 4DPET volume obtained by the 40% threshold method was 7.1 cm³, which was 9% larger than that for 3DPET. The average 4DPET volume (defined as the average six-phased 4DPET volume for all tumors) obtained by MIP was 8.3 cm³, which was 28% larger than that for 3DPET. The average six-phased 4DCT volume for each tumor was larger than that of 3DCT for each tumor. The average 3DCT volume for all tumors was 10.4 cm³, the average 4DCT volume (defined as the average six-phased 4DCT volume for all tumors) was 12 cm³, and the average 4DCT volume was 15.4% larger than that of 3DCT ($p = 0.99$).

The results of the average six-phased 4DPET volume, 3DPET volume, average six-phased 4DCT volume and 3DCT volume of 10 tumors are reported in Figure 2. The PET volume was smaller than the CT volume for both 3D and 4D. The average 4DPET volume was 22.8% larger than the average 3DPET volume ($p = 0.96$) and the volume ratio was 1.23. The average 4DCT volume was 15.4% larger than the average 3DCT volume and the volume ratio was 1.16. The average 4DCT volume was 59.5% larger than the average 4DPET volume ($p = 0.94$).

2.2 | Relationship between tumor motion amplitude, the PET volume, and the CT volume

The 4D volume was more representative of the actual respiratory trajectory, whether it was PET or CT. The comparison of the average 4DPET volume, the average 4DCT volume, and the 3DCT volume with the change of tumor motion amplitude is shown in Figure 3. The volume of 3D PET was not compared because its volume was the smallest of all CT and PET volumes (see Figure 2) and our purpose was to compare the difference between 4DPET, 4DCT and regular scanning 3DCT.

| Tumor | Location | Motion amplitude (mm) | VOL3DPET (cm³) | VOL4DCT (cm³) | VOL3DCT (cm³) | VOL4DCT (cm³) |
|-------|----------|-----------------------|----------------|--------------|--------------|--------------|
| 1     | Upper lung | 1.7                   | 3.6            | 4.2          | 3.6          | 5.0          | 5.9          |
| 2     | Upper lung | 2.0                   | 4.5            | 4.7          | 4.6          | 11.8         | 12.8         |
| 3     | Lower lung | 3.0                   | 8.5            | 9.0          | 10.0         | 12.8         | 14.4         |
| 4     | Middle lung | 3.8                  | 2.1            | 2.2          | 2.3          | 2.5          | 2.9          |
| 5     | Upper lung | 4.1                   | 7.0            | 7.4          | 8.1          | 12.1         | 13.7         |
| 6     | Lower lung | 4.6                   | 1.6            | 2.4          | 3.2          | 3.3          | 4.0          |
| 7     | Lower lung | 4.6                   | 14.0           | 14.3         | 14.9         | 21.0         | 22.5         |
| 8     | Middle lung | 5.6                  | 6.2            | 7.0          | 7.2          | 9.7          | 11.2         |
| 9     | Lower lung | 6.4                   | 10.0           | 11.9         | 16.5         | 14.2         | 18.2         |
| 10    | Lower lung | 7.1                   | 7.0            | 8.2          | 12.3         | 11.8         | 13.9         |

MIP, maximum density projection; VOL3DCT, target volume of 3DCT scan; VOL3DPET, target volume of 3DPET scan; VOL4DCT, target volume of 4DCT scan; VOL4DPTET, target volume of 4PET scan.
caused by breathing exercises. When the tumor motion amplitude was more than 3 mm, the volume difference of 4DCT and 4DPET was 27%. When the motion amplitude was greater than 3 mm and less than 5 mm, the larger the tumor volume was, the larger the ratio of the 4DCT volume to the 4DPET volume: the maximum value was 1.54. When the tumor motion amplitude was greater than 5 mm, the ratio was about 1.4. When the 3DCT volume was larger than 5 cm³, the ratio of the average 4DCT volume to the average 4DPET volume was 1.9. When it was lower, the ratio was almost equal to 1.

2.3 Comparison of the target areas and dose in the lung and heart among ITV3DCT, ITV4DCT_, ITV4DPET_ave, and ITV4DCT_ave

We delineated the target area of 4DPET and 4DCT for six bins, and then obtained ITV4DPET_ave and ITV4DCT_ave by intersection. The difference between 4D scan and 3D scan is that breathing movement is already taken into account for 4D. Gross tumor volume (GTV)3DCT is the target area of 3DCT used in conventional positioning scanning. Generally, doctors expand 1.2 mm, 0.6 mm, and 0.8 mm in the superior-inferior (SI), left and right (LR), and anterior and posterior (AP) directions, respectively, to get ITV3DCT. It is not necessary to consider the external expansion from ITV to plan target volume (PTV) because the external expansion is the same, so it can be ignored uniformly. The method of obtaining the target area ITV3DPET is similar to that for ITV3DCT. The target areas of ITV3DCT, ITV3DPET, ITV4DCT_ave, and ITV4DPET_ave for one tumor are shown in Figure 4. The four target areas were used to make the treatment planning on the conventional 3DCT data optimize until the target area dose reached D95% = 96%, then the doses dose line of 2000 covered the volume of unilateral lung (V20) and dose line of 500 covered the volume of unilateral lung (V5) of the lung and dose dose line of 3000 covered the volume of heart (V30) of the heart were compared. It was found that doses V20 and V5 of ITV3DPET, ITV4DPET_ave, and ITV4DCT_ave in the lung were significantly lower, about 4% and 5%, than those of
3 | DISCUSSION

To ensure that the target tissue will not be missed in the movement during the treatment process, doctors have to increase the expansion around the clinical target volume when sketching the target area, which comes from the instantaneous acquisition of images. 4DCT has been widely studied in target area delineation, including the change of volume and SI, LR, and AP directions. It has been reported that 4DCT cannot be fully applied to the tumor in the state of respiratory motion in radiotherapy. The larger the respiratory motion amplitude of the tumor, the more random the motion artifacts, and 4DCT significantly underpredicted treatment target motion ranges. Respiratory gating (RG) PET/CT technology could affect the target PTV volume of lung cancer patients. PET/CT significantly reduced the geometric loss of PTV volume due to respiratory movement. A difference in dose caused by the difference in target area between 4D PET/CT and 3D PET/CT has also been reported. However, there has only been one report on the volume of 4D PET and 3D PET, in which the change of tumor motion amplitude and volume difference were mentioned.

When delineating the target area on the PET image, the selection of threshold method was involved. Some studies report that the threshold method and standardized uptake value (SUV) were used, and others report that clinical data such as tumor size, background and clinical data including conventional images were considered. In this study, the latter was selected for sketching.

In this study, 10 tumors were studied by RG PET/CT. It was found that the average 4D PET volume measured by two methods was 22.8% larger than that of 3D PET. The ratio of the average 4DCT volume was 15.4% larger than that of 3DCT, and the volume ratio was 1.16, which was close to the value in the literature (1.60 ± 0.55). The PET volumes of all tumors were smaller than those of CT, whether in 4D or 3D. The average 4DCT volume was 59.5% larger than that of 4D PET. It was showed that a volume difference between 3D and 4D technology was obvious because 4D is the integration of captured images of multiple respiratory cycles, while 3D is the instantaneous image. The target volume seemed to be overestimated by 4D CT, while the average 4D PET volume which was the role of tumor metabolism imaging was more possible representative of the actual breathing trajectory.

When the movement amplitude was larger than 3 mm, the volume difference of 4D CT and 4D PET was 27%, which was close to the 54% reported in the literature. When it was more than 3 mm but less than 5 mm, the larger the tumor volume, the larger the volume ratio of the average 4DCT volume to the average 4D PET volume, the maximum value was 1.54. When the conventional 3DCT volume of the tumor was more than 5 cm³, the ratio of average 4DCT volume to average 4D PET volume was 1.9. This shows there is a close relationship between tumor movement amplitude and volume: when the movement amplitude is greater than 3 mm, the relative volume difference is more than doubled. The larger the tumor volume, the greater the ratio of the average 4DCT volume to the average 4D PET volume. This is because the larger the amplitude and volume, the larger the tumor deformation. The target volume seems to be overestimated by 4DCT, and the average 4D PET volume which was according with the biological characteristics of malignant tumors could better represent the actual target volume.

GT V3DCT is delineated using routine 3DCT scanning. Generally, a certain range will be expanded on GT V to avoid missing the target area in treatment due to respiratory movement, and the planning target area ITV3DCT was much larger than that of ITV3D PET, intersected ITV4DCT ave, and ITV4D PET ave, the dose V20 and V5 of normal lung tissue, and the dose V30 of heart were increased accordingly for the planning target area ITV3DCT. Among them, the dose of lung and heart of ITV4D PET ave was the lowest. The reason was that the volume of ITV4D PET ave target area was the smallest, and the volume of the field passing through the lung during irradiation was relatively the lowest. Therefore, compared with 3DCT, the average multiphased 4D PET volume was more suitable for reducing the lung irradiation in clinical radiotherapy.

In conclusion, to delineate lung tumor targets at various positions, particular attention should be paid to the effect of breathing exercises on large movements and large volumes. The target volume seemed to be overestimated by 4DCT, thus the average multiphased 4D PET volume could be used to delineate the tumor target more accurately and reduce the radiation dose of the lung.

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