Radiation dosimetric influence by different target volume definition in Cyberknife lung cancer and abdomen stereotactic body radiotherapy

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**ABSTRACT**

**Purpose:** The dosimetric characteristics between four-dimensional with end-expiration and end-inspiration CT dose distributions of Cyberknife are to be evaluated.

**Methods:** A set of four dimensional (4D) CT images and two sets of CT scans, including end-inspiration and end-expiration breath-hold, were obtained from 15 CyberKnife treated patients. Three internal target volumes (ITVs) were created from the three sequence images. All patients were treated using ITV-based strategy with an additional ITV-to-PTV margin of 3 mm.

**Results:** In all of the 15 patients, the PTVFuse consistently has the smallest volumes compared to other PTVs. The NCI and coverage of the plans were based on PTVFuse, which provided statistically significant differences for PTV4DE and PTV4DI. Additionally, the dose of normal tissue showed no statistical differences in the three type of plans (plan PTV4DE vs PTV4DI, p = 0.76), (plan PTV4DE VSPTVfuse, p = 0.23) and (plan PTV4DI VSPTVfuse, p = 0.16).

**Conclusion:** The fusion of breath-hold sequences is beneficial to provide excellent target coverage than the end-inspiration or end-expiration with 4D-CT approach for target definition. Furthermore, the fusion of the end-expiration and end-inspiration CT scans may be used as an alternative to 4D CT in the absence of multi-modality images.

1. **Introduction**

Cancer remains one of the most common causes of death. The rapid increase of incidence and the type of cancer around the world, which cause the demand for more precise treatments modalities. Radiotherapy (RT) is a cornerstone in the management of lung and abdomen cancer patients. However numerous tumors, including lung cancer, liver cancer, and retroperitoneal region tumor are affected by respiratory movement and gastrointestinal peristalsis, so treating such cancer lead to target moving phenomena (Tokihiro et al., 2008). Meanwhile, the rapid development of radiotherapy technology and Stereotactic Body Radiation Therapy (SBRT) offer hypofractionated (>500cGy/fraction, 1–5 fractions), high conformation, and precision radiotherapy, however the tumors which in the particular areas constraint the clinical application of SBRT and increase its toxicity (Seppenwoolde et al., 2011). Therefore, the administration of SBRT requires high accuracy and precision positioning to the tumor.

CyberKnife (Accuray, Sunnyvale, CA, USA) is an image-guided 6 MV flattening filter-free linear accelerator (LINAC) mounted on a computer-controlled 6-axis robotic arm, it is a typical SBRT treatment technology. The treatment of Cyberknife for the tumors which are affected by respiration is to synchronize the respiration by implanting the gold fiducial around tumors. However, the synchronization technique do not apply to the patient who can not implanted with gold fiducial which easily to cause pneumothorax. In addition, the irregular shape and the density of the tumors also limit the application of the CyberKnife Xsight Lung Tracking System, such patients are restricted when choosing Cyberknife technique (Chan et al., 2013).

In SBRT, the Gross Tumor volume (GTV) and Clinical Target volume (CTV) are considered to be identical for metastatic lung, liver, and paraspinal tumors (SH Benedict et al., 2010). In contrast, there is a small microscopic extension in tumor volume around the GTV in some patients. Organ motion due to respiration is a crucial factor for defining planning target volume (PTV) (Keall et al., 2010; L Wang et al., 2009), therefore, the definition of the PTV is essential.

In our research, we scan the end-expiration, end-inspiration, and the four-dimensional (4D) real-time motion images to track those patients who are unable to use synchronous tracking method and xgigt lung tracking but can benefit from CyberKnife. All patients were positioning by the three methods, and using
spine tracking method in the process of the treatment. Our main purpose is to investigate tumor motion amplitudes based on the coverage of the PTVs and the dose of the normal tissue. Furthermore, we aim to determine the optimum approach for patient-specific tumor motion during SBRT for chest and abdomen cancer.

2. Material and methods

2.1. Patients

In this study, 15 patients with lung and abdomen tumors were recruited for the study between April 2019 and August 2020, and patient characteristics are summarized in Table 1. All patients received CyberKnife treatment for lesions. Written informed consent was obtained from each patient, and all studies involving people, medical records were approved by the Clinical Research Ethics Committee.

2.2. CT scanning

Before CT scanning, all the patients must receive respiratory training. They were laid in the supine position and immobilized in a customized vacuum body mold with their arms along their sides.

Three CT scan sequences, including the end-expiration, the end-inspiration, and 4D-CT of tumors with 1.5 mm thickness were acquired for all patients. During the CT images acquisition, the respiratory signal was recorded with the Philip TumorLOC module (Langner & Keall, 2009).

2.3. Target delineation

The targets were delineated in the end-expiration and the end-inspiration sequences for those which were consistent with those defined in the International Commission on Radiation Units (ICRU) Report 83 (Hodapp, 2012), GTV_{4DE} (GTV was defined in the end-expiration), GTV_{4DI} (GTV was defined in the end-inspiration), and Organ at Risk (OAR). No margins for microscopic extension were added (CTV = GTV). The outer boundary of GTV_{4DE} and GTV_{4DI} were determined by the four-dimensional motion of the targets to developed ITV (internal target volume)_{4DE}, ITV_{4DI}. With the ITV-based strategy, the PTVs were designed to encompass the whole respiratory tumor motion area using an additional generic margin to account for other treatment uncertainties, named as PTV_{4DI} (PTV was defined in the end-expiration) and PTV_{4DE} (PTV was defined in the end-inspiration) (Shih et al., 2004). In our analysis, 'motion amplitude' referred to the vector length calculated from the tumor peak-to-peak amplitudes measured in the left-right (LR), Anterior-Posterior (AP) and craniocaudal (CC) directions. The motion amplitude was measured Philip TumorLOC module, the mass center of the tumor was selected and calculate the max shift of the center through the module. The motion amplitudes of 4D-CT are listed in Table 2.

GTV_{fuse} was created by the fused GTV_{4DE} and GTV_{4DI}, in this method, the ITV_{fuse} = GTV_{Fuse}, ITV_{4DE} and ITV_{4DI} were created through the max respiration amplitude by 4DCT. All patients were treated using an ITV-based strategy with an additional ITV-to-PTV margin of 3 mm. The targets are shown in Figure 1. The margin of the GTV to ITV is different from the other, but the same of the margin standard.

2.4. Treatment planning

The treatment planning system (TPS) for CyberKnife used in this study is MultiPlan 2.4.1.

All CT images and contours were transferred to the CyberKnife TPS (Multiplan 2.4.1, Accuray Inc, USA). The treatment plans were performed on the PTV_{4DI}, PTV_{4DE}, and PTV_{fuse} by non-isocentric planning design method. Three plans were designed on PTV_{4DI}, PTV_{4DE}, and PTV_{fuse}, which were named Plan PTV_{4DI}, Plan PTV_{4DE}, and Plan PTV_{fuse} respectively. The SBRT plans were designed using non-isocenter treatment method. A total doses of 35 to 54 Gy in 4 to 6 fractions were

Table 1. Patient and treatment characteristics.

| Characteristics   | No. of patients |
|-------------------|-----------------|
| Patients          | 15              |
| Age (yr), median (range) | 64(29–89) |
| Gender            |                 |
| Male              | 14              |
| Female            | 1               |
| Tumor location    |                 |
| Upper pulmonary lobe | 9              |
| Middle pulmonary lobe | 1              |
| Lower pulmonary lobe | 1              |
| Abdomen           |                 |
| Pancreatic cancer | 2               |
| Adenocortical carcinoma | 1              |
| Retroperitoneal lymph node | 1             |
| Tumor size        |                 |
| ≤4 cm             | 4               |
| >4 cm             | 11              |

Table 2. The motion amplitudes of 4D-CT by the Philip TumorLOC module and the Prescription of treatment.

| Number | Left-right | Anterior-posterior | Inferior-superior | Prescription(Gy) | fractions |
|--------|-----------|-------------------|------------------|-----------------|-----------|
| 1      | 5         | 5                 | 7                | 40              | 5         |
| 2      | 3         | 3                 | 3                | 40              | 5         |
| 3      | 2         | 2                 | 3                | 40              | 5         |
| 4      | 3         | 3                 | 3                | 40              | 5         |
| 5      | 3         | 3                 | 5                | 35              | 3         |
| 6      | 5         | 5                 | 10               | 48              | 3         |
| 7      | 3         | 3                 | 5                | 50              | 5         |
| 8      | 3         | 3                 | 3                | 50              | 5         |
| 9      | 3         | 3                 | 3                | 40              | 6         |
| 10     | 5         | 10                | 5                | 45              | 5         |
| 11     | 4         | 4                 | 6                | 48              | 3         |
| 12     | 5         | 5                 | 15               | 45              | 5         |
| 13     | 4         | 5                 | 5                | 42              | 6         |
| 14     | 3         | 3                 | 4                | 20              | 4         |
| 15     | 3         | 4                 | 4                | 52              | 4         |
prescribed for targets. The prescription dose to the PTV and the OAR dose constraints were as follows: 90% of PTV received 100% of the prescription dose at least, dose constraints followed Task Group 101 recommendations for normal tissue (S H Benedict et al., 2010). The maximum dose within the PTV was approximately 120% of the prescribed dose.

2.5. Planning evaluation

2.5.1. Contour deformation of different CT sequences using contour-based deformable image registration

As contour quality and volume are critically important in terms of dose evaluation, the volumes of contour were confirmed both via visual inspection and quantitatively. And comparing the volume and quality of the different contours can be achieved by registration and the repeatability of the three contours were scored as suggested in the American Association of Physicists in Medicine (AAPM) Report 132 (Brock et al., 2017). The dice similarity coefficient (DSC) was the quantitative method employed. The DSC is defined as twice the overlapping volume of the ITV at the fusion of the phase and the ITV of the end-expiration, end-inspiration phases by the total volume of both contours. We considered that a DSC >0.7 reflected contour repeatability. A representative comparison of ITV contours is shown in Figure 2.

\[
\text{DSC}(A,B) = \frac{2(A \cap B)}{(A + B)} \tag{1}
\]

A and B represented two contours, As the contours approach agreement, the DSC value approaches 1; As the volumes diverge into two non overlapping structures, the DSC value goes to zero. However many professional literature obtained that the values of DSC>0.700 shows optimum overlap of contours (Nelson et al., 2020; Sang et al., 2019).

2.5.2. Planning parameters evaluation

CyberKnife plans were compared between 4D-CT scans with two extreme breath-hold sequences. Three plans were evaluated for dose conformity index (CI), New conformity index (NCI) (Patel et al., 2020), and coverage (percentage of target volume exceeding prescription dose to tumor volume) to the target volume (Neill, 2014). The Monitor units (MUs) and normal tissue dose were also compared.

CI mainly evaluates the minimum prescription dose of the target, \( CI = \frac{TV_T}{TV_p} \) (TV is the all tissue volume covered by the prescription line. Where TV is the Target Volume, the target volume is covered by the prescription dose. For the CyberKnife treatment planning design, the value is usually 1.1–1.5. The ideal coverage is achieved when CI = 1. A paired t-test was used for the three plans.

Occasionally, the prescription dose line is tight and covers all the tumor volume, and with the value of CI = 1; however, the prescription line did not

Figure 1. The targets were generated based on three sequences. A: the targets definition of the fusion of the end-expiration and end-inspiration, \( ITV_{\text{Fuse}} = GTV_{\text{fuse}} \); B: the targets definition of the end-expiration based on 4D-CT, \( ITV_{4\text{DE}} \) was created through the max respiration amplitude by 4DCT; C: the targets definition of the end-inspiration based on 4D-CT, \( ITV_{4\text{DI}} \) were created through the max respiration amplitude by 4DCT; the margin of ITV-to-PTV is 3 mm.

Figure 2. A representative internal target volume (ITV) contour at the end-expiration and end-inspiration sequences. The GTV at the end-expiration was shown in Red. The GTV at the end-inspiration was shown in Pink. The GTV of the fuse of the two sequences was shown in Yellow.
completely cover the target volume (Lo et al., 2020). Thus, nCI was introduced to consider CI and coverage together, $nCI = \frac{CI}{\text{coverage}}$, a paired t-test was used to compare the nCI of three treatment plans.

3. Results

3.1. Assessment of contour repeatability accuracy

Figure 2 showed the repeatability of the three sequences and the variances by the effects of respiration in the targets, the DSC for each patient were showed in the Figure 3. The DSC met our criteria (DSC > 0.7).

3.2. Target volume variation

For each patient, the center of mass of the PTV4DE, PTV4DI, or PTVfuse may be different from each other due to changes in volume and shape. We first compared GTV volumes from the end-expiration and end-inspiration sets of CT scans, as shown in Figure 4. Due to the solid tumor, the volume of the tumor changes irregularly at the end-expiration and the end-inspiration. A paired t-test confirmed that they are no statistically significant ($p = 0.73$).

The resultant PTV volumes were also compared, as shown in Figure 5. There were no statistical difference with each other, $\text{PTV}_{4\text{DE}}$ VS $\text{PTV}_{4\text{DI}}$ ($P = 0.358$, $t = 0.95$), $\text{PTV}_{4\text{DE}}$ VS $\text{PTV}_{\text{fuse}}$ ($P = 0.16$, $t = 1.47$), and $\text{PTV}_{4\text{DI}}$ VS $\text{PTV}_{\text{fuse}}$ ($P = 0.17$, $t = 1.42$).

3.3. Impact of PTV design on treatment planning

We next studied the impact of different PTV designs on treatment planning and dose normalization of the PTV.

CI and NCI and were initially compared. From Table 3, the CI of the GTVs in end phase had difference from the fuse method; for NCI, Plan $\text{PTV}_{4\text{DE}}$ VS Plan $\text{PTV}_{4\text{DI}}$ ($t = -0.16$, $P = 0.87$), Plan $\text{PTV}_{4\text{DE}}$ VS Plan $\text{PTV}_{\text{fuse}}$ ($t = 2.29$, $P = 0.04$) and Plan $\text{PTV}_{4\text{DI}}$ VS Plan $\text{PTV}_{\text{fuse}}$ ($t = 2.27$, $P = 0.039$), the value of end-expiration and end-inspiration had no statistical difference while all had statistical difference with the fusion plans.

MU comparison shows that most (90%) of the fusion plans exhibited higher MUs than the end-expiration and end-inspiration plans. A paired-samples t-test was used to compare the three plans. The end-expiration and the end-inspiration of all plans had a significant difference with the fusion plan. The dose distribution of all targets is shown in Table 3.

Coverage (%) is the percentage of target volume covered by the prescription dose line. We compare the coverage to PTV and GTV. A paired-samples t-test was used to compare the three plans. The

![Figure 3](image3.png)\(\text{Figure 3.}\) The DSC for each patient and the max respiration amplitude.

![Figure 4](image4.png)\(\text{Figure 4.}\) The Volume of GTV of the end-expiration and end-inspiration.
Figure 5. The Volume of PTV of 4DCT and the fusion of the phases.

Table 3. The statistic analyze of dose distribution of the targets: CI and NCI represent GTV.

|                | CI     | NCI    | MU   |
|----------------|--------|--------|------|
| PTV4DE VS PTV4DI | −1.14  | 0.66   | 2.44 |
| t value         | 0.272  | 0.516  | 0.02 |
| P value         | 0.00   | 0.00   | 0.00 |

Table 4. The coverage of PTVs and GTVs.

| Coverage-PTV | Coverage-GTV4DE | Coverage-GTV4DI |
|--------------|-----------------|-----------------|
| PTV4DE VS PTV4DI | −0.72          | 0.54            |
| t value       | 0.48            | 0.61            |
| P value       | 0.00            | 0.00            |
| PTV4DE VS PTV4DI | −0.51          | 1.8             |
| t value       | 0.09            | 0.16            |
| P value       | 0.00            | 0.00            |
| PTV4DE VS PTV4DI | −0.75          | −2.3            |
| t value       | 0.037           | 0.003           |
| P value       | 0.00            | 0.00            |
| PTV4DE VS PTV4DI | −0.75          | −2.75           |
| t value       | 0.003           | 0.0015          |
| P value       | 0.00            | 0.00            |
| PTV4DE VS PTV4DI | −0.75          | −1.85           |
| t value       | 0.003           | 0.08            |
| P value       | 0.00            | 0.00            |
| PTV4DE VS PTV4DI | −0.75          | −2.4            |
| t value       | 0.003           | 0.00            |
| P value       | 0.00            | 0.00            |
| PTV4DE VS PTV4DI | −0.75          | −3              |
| t value       | 0.003           | 0.00            |
| P value       | 0.00            | 0.00            |

three plan shows no statistical difference, as shown in Table 4. However, the coverage of the GTVs of the end-expiration and end-inspiration show significant differences. For the coverage of the GTV 4DE, Plan 4DE VS Plan4DI (t = −2.3, P = 0.037), Plan4DI VS Plan 4DI (t = −2.75, P = 0.015); For the coverage of the GTV 4DE, Plan4DE VS Plan 4DI (t = −2.4, P = 0.00), Plan 4DI VS Plan4DI (t = −3, P = 0.00).

3.4. Impact of OAR on treatment planning

Among the 15 patients, 11 patients have lung lesions, and 4 were suffering from abdominal lesions. Due to a lack of patients, the paper did not analyze the dose of OARs in abdominal lesions. We compared the V20 (volume receiving more than 20 Gy) and 10 (volume receiving more than 10 Gy) for normal lung tissue between Plan PTV 4DE, Plan PTV 4DI, and Plan PTV 4DI. The differences were analyzed by the paired t-test. The dose evaluation of normal tissue is listed in Table 5.

4. Discussion

CyberKnife is a new treatment technology in stereotactic radiosurgery. The linear accelerator can produce a 6 MV X-ray to trace the tumors in real-time throughout the body. CyberKnife is currently the only device in radiotherapy to track breathing motion in real-time, with a tracking accuracy of up to 1.5 mm. The respiratory tracking method is mainly based on the gold fiducial markers, which are implanted into the center of the tumor to replace the tumors’ movement. Meanwhile, it establishes a correlation model with respiratory signals on the body surface to achieve real-time tracking. However, in a clinical setting, fiducial
markers’ implantation can lead to pneumothorax. Consequently, the patients cannot use the real-time tracking of CyberKnife radiotherapy (Li et al., 2019). In the paper, we optimized the positioning methods for ineligible patients to reduce the errors caused by breathing and reduce the target area’s leakage.

Respiratory motion affects all tumor sites in the thorax and abdominal region during radiotherapy. It is worthy to note that respiratory motion is one potential source of error in radiotherapy. (Ekberg et al., 1998) found that the average GTV movement with quiet respiration was about 2.4 mm in the mediolateral and dorso-ventral directions, and the average movement in the cranio-caudal direction was 3.9 mm with a range of 0–12 mm. The results of these previous studies are in well agreement with our current finding shown in Table 2. The methods used to manage respiratory motion in radiation oncology mainly include motion encompassing methods, respiratory-gated techniques, breath-hold techniques, forced shallow breathing methods, and respiration-synchronized techniques (Keall et al., 2006). Even so, current advancement cannot establish methods that explicitly account for respiratory motion (Descovich et al., 2015). The important methods for obtaining high-quality CT data of respiratory motion are 4D CT or respiration-correlated CT, such as end-expiration and end-inspiration. Four-dimensional data are analyzed to determine the mean tumor position and the tumor motion range for treatment planning. However, (Liang et al., 2018; Liu et al., 2007) showed that 4DCT might fail to accurately estimate the tumor motion due to several factors, including irregular breathing, short acquisition time, and/or anatomical changes between simulation and treatment. The motion of the four-dimensional CT qualitatively analyzed the influence on the volume of the target area. From the Figure 3, it can be seen that the volume of the target area in the three plans was different with each other greatly when the amplitude was big of the patient, and the DSC values of patient6 and patient12 were lower than 0.7 due to the great respiration amplitude.

We mainly used three CT localization sequences, including end-expiration, end-inspiration, and real-time scanning sequence of 4D-CT to study the dose evaluation of treatment planning on three CT methods in CyberKnife Stereotactic radiotherapy. The 4D-CT was mainly used to locate the respiratory amplitude of the tumor center. All these data were normalized to their planned values by comparing the ratios of the dosimetric parameters of the GTVs in each plan. We aimed to investigate that which PTV definition provided the optimum GTV coverage during the treatment plan and reduced the likelihood of potential target leakage (Bushra, 2019).

The volume of GTVs was different between end-expiration and end-inspiration, and respiration can lead to the deformation of the tumors, as shown in Figure 4. The PTVs had a larger volume difference because of the different PTV generation methods. We found that the PTV4D consistently resulted in the smallest volumes compared with the other PTVs (p = 0.16 and \( p = 0.17 \)), but show no significant difference with each other. Generally, the plans based on PTV4D could provide promising target conformity for PTV4DE and PTV4DI (p = 0.04 and p = 0.039), and show statistical difference. With dose normalization of the PTVs, the coverage of PTV4D returned to 4D and PTV4D reached the high coverage of targets, with the P values of 0.61, 0.59, and 0.48, respectively. However, the coverage of GTV4DE and GTV4D in plan PTV4DE (p = 0.037 and p = 0.015) and plan PTV4DI (p = 0.00 and p = 0.00) showed lower coverages than the plan PTV4D and were statistically different. Table 3 and Table 4 also showed that the plan based on end-expiration and end-inspiration are statistically different from the fusion of the two sequences, indicating that it is related to the changes of the volume and the shapes of the PTVs. The nCI and MU of the target were changed under the constant selection of the collimators. Many existing studies employed technique of 4DCT treatment and multi-phase scanning. Pramod Kumar Sharma et al. (Pramod et al., 2016) compared the delineation and treatment planning of 2 Phase based (end-expiration and end-inspiration) internal gross tumor volume (IGTV) with 10-phase based (four-dimensional [4D]). This study had given the guidance of the paper; the result indicated the excellence application in the upper lung cancer and the contour as well as the dose without big difference.

Additionally, due to high dose falloff of CyberKnife, the dose of the normal tissue had no differences in three type plans (plan PTV4DE VS PTV4DI, \( p = 0.76 \)), (plan PTV4DE VS PTV4D, \( p = 0.23 \)) and (plan PTV4D VS PTV4D, \( p = 0.16 \)). However, the lung tissue of the fusion-based plan of the two sequences was generally lower than the other

### Table 5

| Patient Number | V20 or V10 (%), PTV4DE | V20 or V10 (%), PTV4DI | V20 or V10 (%), PTV4D |
|----------------|------------------------|------------------------|------------------------|
| 2              | 13.86                  | 16.74                  | 16.74                  |
| 3              | 11.16                  | 11.16                  | 11.16                  |
| 4              | 12.63                  | 12.35                  | 12.65                  |
| 5              | 16.06                  | 16.06                  | 16.75                  |
| 6              | 19.78                  | 19.78                  | 15.24                  |
| 7              | 19.78                  | 19.78                  | 15.24                  |
| 8              | 23.25                  | 20.28                  | 20.8                   |
| 9              | 20.12                  | 20.12                  | 12.0                   |
| 10             | 8.52                   | 8.52                   | 5.61                   |
| 11             | 8.7                    | 8.7                    | 5.6                    |
| 15             | 8.1                    | 8.1                    | 6.2                    |
| t              | 0.312                  | 1.26                   | 1.53                   |
| p              | 0.76                   | 0.23                   | 0.16                   |

V20, volume receiving more than 20 Gy; V10, volume receiving more than 10 Gy

The table shows the comparison of different PTVs in terms of volume receiving more than 20 Gy and 10 Gy. The values are presented as percentages. The t-test values (t) and p-values are also provided to indicate the statistical significance.
two methods, as listed in Table 5. The values of the five, ten, and 15 had maximum differences in the normal lung tissue. Our result also showed that the three patients’ respiration motion amplitudes were very large, with over 1 cm so that the margins would include more lung tissues. This result contrast with the findings of Wang et al (Z Wang et al., 2011), which may be related to the selected treatment equipment, and future diagnostic systems can be based on deep learning (Shi, Yuguang, Zhu, Lianta, Huang, Huang et al., 2020; Tang et al., 2021; Wong et al., 2020) and big data analysis (Yuguang et al., 2021) in order to improve evaluation of treatment planning on the patients.

5. Conclusion

In this paper, we found that the three plans based on the three defined targets achieve their clinical goals. And the fusion of the end-inspiration and end-expiration breath-hold is beneficial to provide excellent target coverage than the end-inspiration and end-expiration breath-hold with a 4D-CT approach for target definition. Taken together, our results suggest that the fusion of the end-expiration and end-inspiration CT scans can be used as an alternative to 4D CT in the absence of multimodality images.

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