The institutional experience of the implementing 4DCT in NSCLC radiotherapy planning

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ABSTRACT

Background: The study was to evaluate the effectiveness of dose distribution of four-dimensional computed tomography (4DCT) simulation.

Materials and methods: The gross tumor volume (GTV) and clinical target volume (CTV) were contoured in all 10 respiratory phases of 4DCT in 30 patients with non-small cell lung cancer (NSCLC). Both 3D and 4D treatment plans were made individually for each patient using the planning volume (PTV). The PTV3D was taken from a single CTV plus the recommended margin, and the PTV4D was taken from the 4D internal target volume, including all 10 CTVs plus the setup margins.

Results: The mean PTV was 460 ± 179 (69–820) cm^3 for 3DCT and 401 ± 167 (127–854) cm^3 for 4DCT (p = 0.0018). The dose distribution (DD) of organs at risk, especially the lungs, was lower for the 4DCT simulation. The V5%, V10%, and V20% of the total lung dose for 4DCT were significantly lower for the 3DCT. However, lung V30% the heart, esophagus, and spinal cord were not significantly different. In addition, the conformity index and the dose heterogeneity index of the PTV were not significantly different. The normal tissue complication probability (NTCP) of the lung and heart was significantly lower for 4DCT than for 3DCT.

Conclusions: The 4DCT simulation gives better results on the NTCP. The organs at risk, especially the lungs, receive a significantly lower DD compared with the 3DCT. The conformity index (CI), heterogeneity index (HI) and the DD to the heart, spinal cord, and esophagus were not significantly different between the two techniques.

Key words: 4DCT simulation technique; 3D-CRT; NTCP; HI; CI

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Introduction

Radiation therapy plays an important role in both curative and palliative treatment of patients with non-small-cell lung cancer (NSCLC) [1]. Radiation therapy benefits more than 75% of patients with NSCLC [2]. Technological developments have greatly reduced the side effects of radiation therapy, especially when performing intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques. However, controlling patient's breathing movement remains challenging [3, 4]. To ensure sufficient coverage of the tumor, the internal margin and the setup margin must be added from the clinical target volume (CTV) to delineate the planning target volume (PTV) [5].
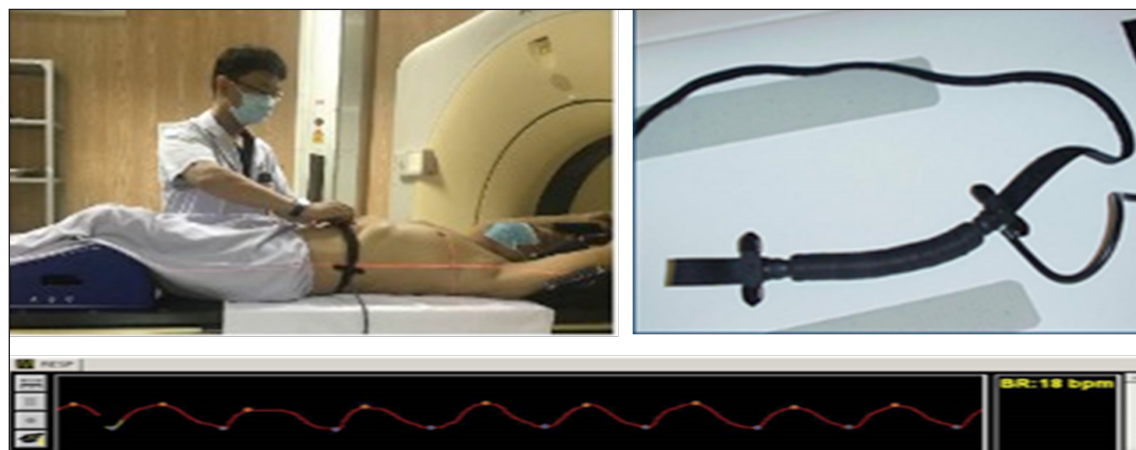
Figure 1. The belt system records the patient's breathing and simulated posture. The breathing pattern appears on the screen of the simulated computed tomography system

The geometric margin of respiratory motion is often based on medical imaging such as X-ray, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)/CT, clinical experience, and recommended values [6]. Geometric margins are not accurate or depend on the characteristics of each patient, so the PTV may be less or more than the volume required for radiotherapy [7]. Four-dimensional computed tomography (4DCT) simulation shows obvious changes in time, anatomical images during simulation, planning, and dose distribution [8]. Theoretically, 4DCT can reconstruct tumor cell mobility in each phase for radiotherapy planning and accurate internal target volume (ITV) generation, which covers the movement range of the CTV. Researchers have recently reported that using 4DCT to determine the ITV for lung cancer could substantially reduce the PTV while safely covering the target [9, 10]. However, this new method has not been widely used to identify the ITV with 10 respiratory stages to evaluate quantitatively the benefit of minimizing dose delivery to organs at risk (OAR) in patients with NSCLC in Vietnam. This study was designed to evaluate the usefulness of 4DCT in reducing the dose distribution and the probability of major organ complications in radiotherapy.

Materials and methods

Criteria for patient selection

The study included 30 patients with histologically confirmed inoperable stage 3 NSCLC, staged according to the TNM system according to the AJCC Cancer Staging Manual (8th edition). Each patient underwent 4DCT simulation with the free breathing technique as shown in Figure 1. The indicated dose was 60 Gy with 30 fractions. The radiotherapy plan was performed with the 3D conformal radiation therapy (3D-CRT) technique (17 patients) and IMRT (13 patients) from December 2020 to July 2022 at the Department of Radiation Therapy, Institute of Oncology and Nuclear Medicine, Military Hospital 175. The data were retrospectively analyzed. Each patient agreed to participate in the study before it began.

4DCT simulation

The Prostep and Wingstep immobilizers were used to improve the imaging-stable reconstruction of patients during daily radiotherapy. Patient data were obtained with a 3 mm slice thickness from the lower end of the cricoid cartilage to the lower edge of the liver. 4DCT simulations were performed using the Philips Brilliance Big Bore CT system (Philips Medical Systems, Highland Heights, OH, United States) while the patient breathed freely. The patient was trained to breathe freely and tracked on the screen to analyze the breathing rate, frequency, and variables before simulation. The Phillip's Air Bellow motion measurement system was placed on the patient during the scan.

Data collection was repeated at each position until the entire longitudinal anatomical image of the region of interest was obtained. The 4DCT

images are arranged into 10 stages according to the respiratory cycle, labeled from CT00 to CT90 (CT00 for the inhalation phase, CT20 for the respiratory-intermediate state, and CT50 for the exhalation phase). Transform anatomy to other AVG10 image set using deformable, projection images of the AVG10 mean phase of 4DCT were reconstructed to delineate the PTV with the 3mm for each slide. The imaging data were then sent to the Elekta Monaco Version 2.4 planning system.

Determination of the planning target volume (PTV)

For PTV_{4D}, the GTV and the CTV were obtained directly from the AVG10 dataset. In this study, the GTV is an image that includes the primary lesion observed on CT and is based on reference some other diagnostic images such as CT scan with contrast injection and/or PET/CT. The GTV was determined based on the mediastinal window image, then re-added and re-edited on the lung parenchyma window. Lymph nodes were considered involved if they were larger than 10 mm, and these regional lymph nodes were identified based on mediastinal window imaging. The ITV in the study of macroscopic and lymph node tumors was determined for each phase of the respiratory process and then aggregated on the average CT image to form the ITV. The CTV includes the volume of the macroscopic tumor and the surrounding microscopic metastases. The CTV was determined by adding the surrounding 5 mm for both the tumor and lymph node according to the European Society for Radiotherapy and Oncology (ESTRO) 2017 criteria. The PTV includes the CTV considering tumor mobility and deviation when placing the patient during radiation therapy. The deviation in patient placement during radiotherapy was averaged at 5 mm. PTV_{4D} was calculated as $CTV_{4D} + 5$ mm in all directions.

For PTV_{3D}, the conventional CT scan phase was the set of routine CT image CT1 which is acquired before the processing of 4DCT simulation. It was calculated with the formula $CTV_{3D} + 10$ mm (front, back, and sides sides) + 15 mm (upper-lower direction).

After delineating the entire radiotherapy Planning Target Volume (PTV) of the two datasets 4DCT and 3DCT, including the organs at risk including the lungs, heart, esophagus, and spinal cord were plotted on two sets of recording data, AVG10 and CT1, for planning.

Planning and evaluation

The 3DCT and 4DCT treatment plans were made in the MONACO system software which use Monte-Carlo algorithm to calculate dose for each patient by using two different PTVs in the (Diagram 1) PTV_{3D} and PTV_{4D}. 3D-CRT and IMRT radiotherapy techniques were performed using the Elekta Precise linear accelerator with a 6 MV or 15 MV photon beam. The indicated dose and field design were identical between the two plans with 7–9 coplanar fields; the indicated dose was 2.0 Gy/fraction. The target dose was at least 95% of the dose that covers the entire PTV_{3D} and PTV_{4D}.

The following information was also recorded: a dose–volume histogram (DVH) of OAR for the 3DCT and 4DCT plans in each patient; the mean lung dose (MLD) values; V5%, V10%, V20%, and V30% of the whole lung; the mean heart dose; the maximum spinal cord dose; and the mean esophageal dose. The normal tissue complication probability (NTCP) was calculated for the lung, heart, and esophagus based on a previous study[11], with the alpha/beta values, the coefficient a, the tolerance dose (TD50), the 50% gamma coefficient, the radiation dose per fraction (Gy), and the total dose fractions presented in Table 1.

Gay et al. [11] proposed a two-step process to calculate the NCTP. First, equivalent uniform dose

Table 1. Results from Emami et al. [19] when healthy tissue tolerates a dose of 1.8–2 Gy/fraction

Organs	TD50 [Gy]	a	50% gamma	Dose [Gy] per fraction	Number of fractions	Alpha/beta
Lung	24.5	1	2	2	30	4
Heart	50	3	3	2	30	2.5
Esophagus	68	19	4	2	30	10

TD50 — tolerance dose for 50% complication probability

(EUD) which was derived on the basis of a mechanistic formulation using a linear-quadractic cell survival model, is calculated as

$$EUD = \left(\sum_{i=1} (v_i \, D_i^a) \right)^{1/a} \quad (1)$$

Where a is a unitless model parameter that is specific to the normal structure of interest, and is unitless and represents the i'th partial volume receiving dose D_i in Gy. Since the relative volume of the whole structure of interest corresponds to 1, the sum of all partial volume will equal 1.

Then, NTCP is calculated from EUD:

$$NTCP = \frac{1}{1 + \dfrac{TD_{50}}{EUD}^{4\gamma 50}} \quad (2)$$

TD_{50} is the tolerance dose for a 50% complication rate at a specific time interval when the whole organ of interest is homogeneously irradiated, and the is a unitless model parameter that is specific to the normal structure or tumor of interest and describes the slope of the dose-response curve.

A program to calculate the percentage of NCTP and EUD using the open-source Python code has been developed and is available from the GitHub open source community (Fig. 2), including the URL https://github.com/ahmedx10/nctp-project.git. The parameters for evaluating the probability

of benign tissue complications were taken from Gay et al. [11].

The DVH and radiotherapy plan evaluation are based on consensus between the medical physicist and physician until the desired plan is reached. Field angles and radiation dose-weighted ratios are used to optimize coverage for the planned target volume and to minimize the radiation dose to the heart, esophagus, and especially the lungs. The lung tumor location depends on the patient and does not always satisfy the requirements for the homogeneity of the isodose line. The conformity index (CI) and the dose heterogeneity index (DHI) were calculated to evaluate the reasonableness and uniformity in the dose distribution [12]. The equations appear below:

$$CI = V_{RI}/TV \quad (3)$$

where V_{RI} is the reference isodose volume (cc) which, according to ICRU, is 95% isodose and the target and TV is the Target volume designated as planned target volume (PTV) (cc);

$$DHI = D \geq 95\%/D \geq 5\% \quad (4)$$

where $D \geq 95\%$ is the dose approaching 95% of the PTV and $D \geq 5\%$ is the dose approaching 5% of the PTV.

Statistics and data analysis

Statistical analysis was performed using Microsoft Excel software with functions in the Data Analysis set. Paired t-tests were used to compare and evaluate the results of volume and dose distribution between plans. The difference was considered significant if $p < 0.05$.
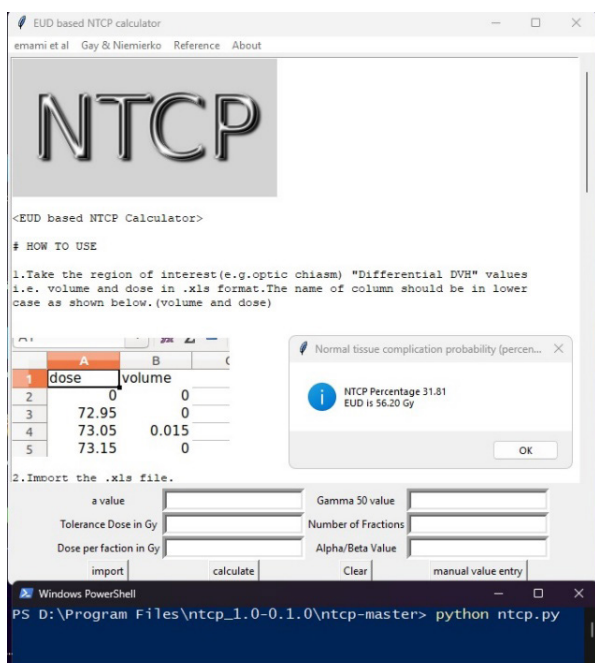
Results

PTV comparison

The mean PTV_{4D} was 401 ± 167 (69–820) cm^3 and the mean PTV_{3D} was 460 ± 179 (127–854) cm^3. On the other hand, the average percentage difference (APD) which is calculated by the absolute

Figure 2. Program used to calculate the normal tissue complication probability (NTCP) in the Python language

$$APD = \left(\frac{PTV3D - PTV4D}{PTV3D} \right) * 100$$

is 21,7% between PTV_{4D} and PTV_{3D} (P = 0.00183, Table 2). In 25 of 30 patients, the PTV_{3D} was larg-

**Table 2.** Comparison of three-dimensional (3DCT) and four-dimensional (4DCT) computed tomography simulation results of vital organ at risk (OAR) doses

Organs	3DCT	4DCT	p
PTV [cm^3]	460 ± 179	401±167	0.0018
Mean lung dose [Gy]	18.3 ± 4.00	16.9 ± 3.30	0.020
V5% [Gy]	59.9 ±12.30	44.6 ± 10.20	0.049
V10% [Gy]	55.8 ±11.70	31.2 ± 6.90	0.008
V20% [Gy]	40.5 ±8.60	28.9 ± 6.90	0.027
V30% [Gy]	28.9 ±6.90	25.3 ± 7.20	0.129
Mean heart dose [Gy]	15.8 ± 16.80	13.1 ±12.20	0.473
Maximum spinal cord dose [Gy]	40.0 ± 6.30	37.9 ± 6.10	0.116
Mean esophagus dose [Gy]	19.1 ± 7.50	18.7 ± 8.02	0.680
NTCP to the lungs (%)	31.75 ± 9.15	26.96 ± 7.40	1.54e-05
NTCP of the heart (%)	11.18 ± 10.02	7.78 ± 6.73	0.0018
NTCP of the esophagus	21.17 ± 10.09	19.45 ± 10.91	0.060
CI	0.62 ± 0.122	0.62 ± 0.164	0.827
DHI	1.09 ± 1.11	1.10 ± 0.03	0.579

PTV — planning target volume; NTCP — normal tissue complication probability; CI — conformity index; DHI — dose heterogeneity index
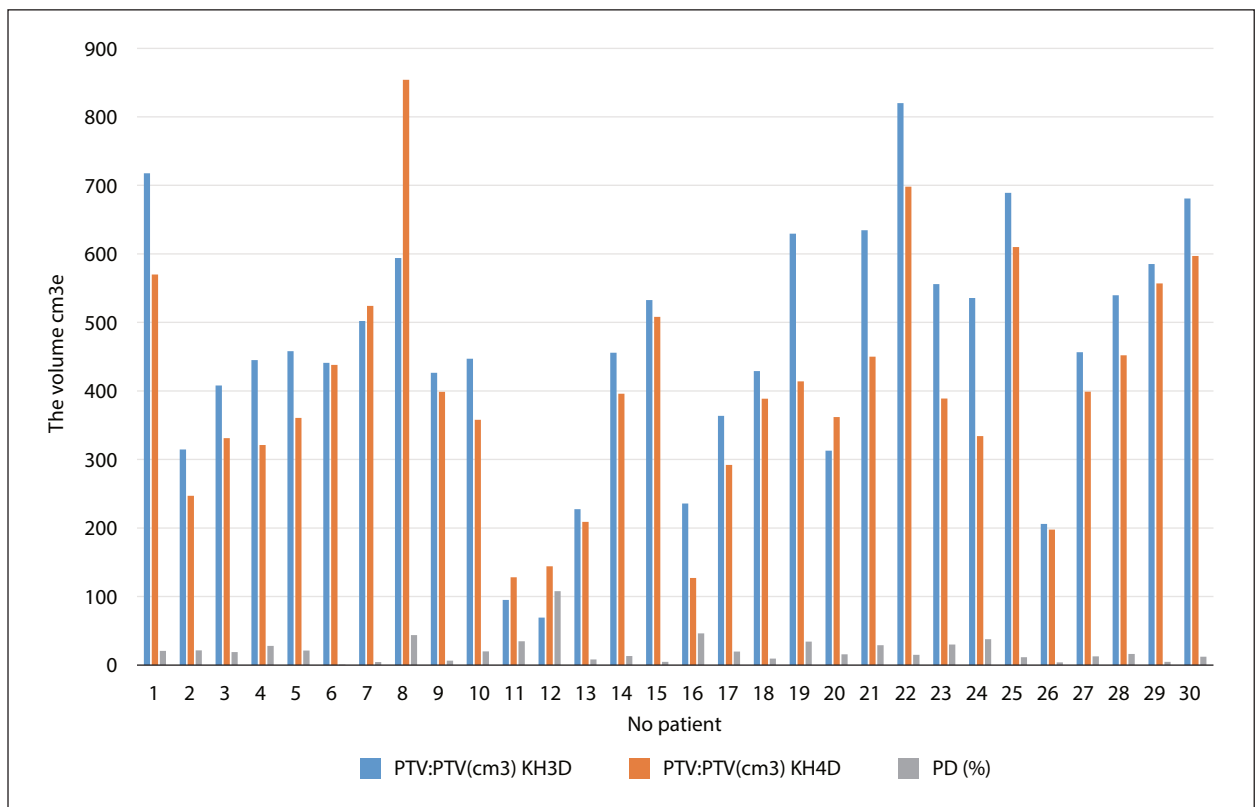

Figure 3. Tumor volume of the three-dimensional (3DCT) and four-dimensional (4DCT) simulations and percent difference (PD)

er than the PTV$_{4D}$ (Fig. 3). The conventional marginal opening added to the CTV for the 3DCT simulation exceeded what was needed and result-

ed in unnecessary irradiation of normal tissues, especially the lungs and spinal cord. Although 5 of 30 patients had a smaller PTV$_{3D}$ to PTV$_{4D}$,
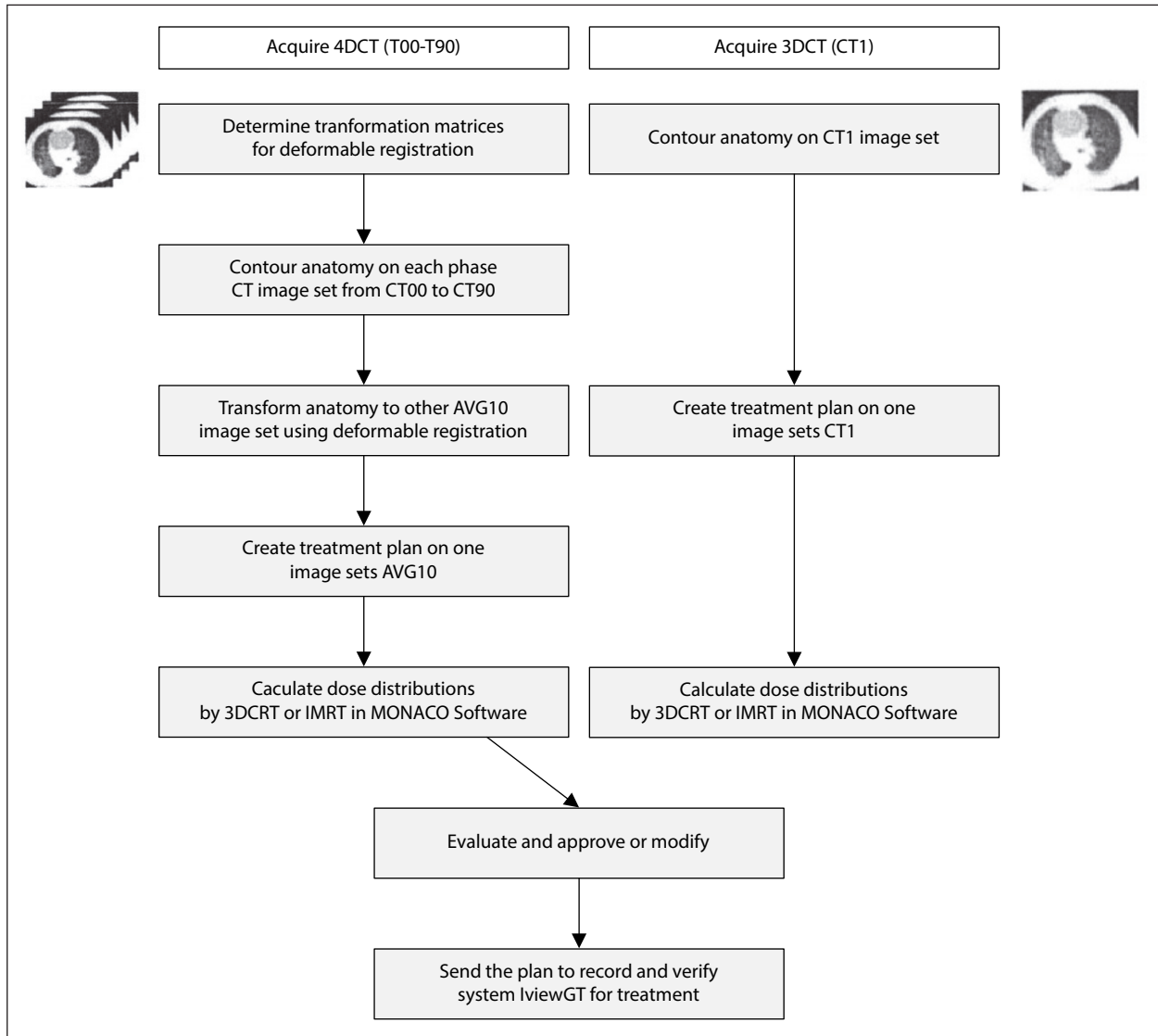
Figure 4. The workfollow of three-dimensional (3DCT) and four-dimensional (4DCT) computed tomography treatment plans were made in the monaco system which use Monte-Carlo algorithm.

the PTV for the 3DCT simulation which may implicate that 3D technique was missing target volume that can be exceeded by the volume required for radiotherapy.

Dose assessment for OAR

Table 2 shows the dosimetric evaluation from the 3DCT and 4DCT simulations. The 4DCT simulation numerically reduced the dose to the lungs, heart, esophagus, and spinal cord. While the maximum dose to the spinal cord, the mean dose to the heart, and the mean dose to the esophagus were not significantly different between the 3DCT and 4DCT simulations ($p > 0.05$), the mean dose to the lungs was significantly higher for the 3DCT

simulation than for the 4DCT simulation ($p = 0.02$). V5%, V10%, and V20% of the lung were significantly higher for the 3DCT than for the 4DCT simulation ($p < 0.05$). There was no significant difference in lung V30% between the 3DCT and 4DCT simulations ($p = 0.129$).

Comparison of the DHI, the CI, and NCTP

The DHI and CI were not different between the two plans ($p = 0.827$ and $p = 0.0579$, respectively (Tab. 2). The NTCP to the lungs was significantly smaller for the 4DCT simulation than for the 3DCT simulation ($p = 1.54\text{e-}05$). The NCTP to the heart was also significantly smaller for the 4DCT simulation than for the 3DCT simulation ($p = 0.0018$).

In contrast, there was no significant difference in the NTCP to the esophagus (p = 0.060). In addition, for the group of patients using the IMRT technique to plan radiotherapy, it was possible to increase the dose of radiation therapy from 4 to 6 Gy depending on the plan, while still limiting the dose to healthy organs.

Discussion

4DCT is a radiotherapy simulation technique that provides more complete information with the addition of a "time" element to conventional 3DCT images. This technology has served as the basis for the development of the 4D radiotherapy method [13, 14]. A 4DCT simulation is useful to track the movement of tumors and normal tissues during radiation therapy. With 4DCT technology, Weiss et al. [15] recorded the change in volume and position of a tumor in the thorax and normal tissues during normal respiration and found that during respiration, marginal volume magnitude increased to 62.5% for the GTV, 25.5% for the lung, and 12.6% for the heart. In this study, the average percentage difference volume between PTV_{3D} and PTV_{4D} is about 21.7%. This may result in underdosing the tumor and overdosing vital organs. However, with the 4DCT technique, tumor healthy organ movements can be recorded and the AVG images are processed by aggregating the average images of the 10 recorded phases. Furthermore, 5 in 30 patients had the PTV_{3D} smaller than PTV4D that can explain missing the target volume and depends on the location of the tumor in the lung. Due to PTV_{3D} being reconstructed each slide of 5 mm and 3 mm for the 4DCT simulation. In lung cancer, there is still much controversy regarding which phase of synthesis is most appropriate when using radiotherapy planning because of electron density concerns. This may cause some errors in the calculated dose results. Sun et al. [16] studied the change in lung volume and its respiratory movement characteristics based on 4DCT and concluded that lung volume on CT at 20%, 30%, and 80% of respiration is the closest to the mean lung volume during free respiration, and the radiation dose distribution values provide reasonable estimates when performed over this period. Compared with inhalation, during exhalation the patient is more comfortable and easier

to perform; therefore, stage 20% (T20) was chosen as the reference image to calculate the dose distribution. However, in this study, we choice AVG10 dataset in order to calculate the dose and realize that there is a difference between them.

After performing 4DCT imaging, the main problem is to identify the target tumor accurately. Rietzel et al. [6] discussed that, when using an open-ended treatment plan for patients with abnormal respiratory movements as recommended, it is possible to omit the target volume requiring radiotherapy or to overdose the volume that does not require radiotherapy. Therefore, for special cases of respiratory function, it is necessary to have an open design target volume for each case. With the 4DCT technique, Rietzel et al. [6] found that comparing a PTV with a margin of 15 mm on a 4D target volume to a PTV with 20 mm on routine 3DCT data resulted in a mean 23% reduction in the target mass size. It is similar to our study where we also noted a 21.7% difference in the PTV when comparing 3DCT and 4DCT. This result indicates that the 3DCT simulation can increase the irradiation area, a finding consistent with the assessment of this study, which should be of interest and importance in NSCLC irradiation. Compared with the 3DCT plan, the 4DCT plan reduces the dose to the lungs, so it is possible to think about increasing the dose for the tumor from 4 to 6Gy while ensuring that the healthy organs still receive an acceptable amount of radiation. Machtay et al. [17] concluded that a biologically effective dose of 1Gy biologically effective dose (BED) provided an approximately 3% relative improvement in locoregional control.

The results of the present study are different than those reported by Tong Bai et al. [18]. Those authors found significant differences between the 3DCT and 4DCT simulations regarding the radiation doses delivered to the heart, spinal cord, and esophagus. There are two reasons for the lack of a significant difference in the present study. First, the patients in this study had large tumor volumes: in many patients, the volume accounted for 30–40% of the ipsilateral lung volume. Second, radiotherapy was performed using two techniques: IMRT (n = 13) and 3D-CRT (n = 17) techniques. We don't use IMRT in all cases. However, the results of pulmonary totals are consistent with other studies.

Based on the NTCP results, the 4DCT plan has a lower risk of normal tissue complications than the 3DCT plan. However, this result is only for theoretical reference; in fact, many factors affect the effectiveness of treatment and side effects for patients.

Conclusion

Using 4DCT simulation for radiotherapy planning in patients with NSCLC reduces the radiation dose volume compared with 3DCT simulation. Additionally, it reduces the dose distribution to the vital organs, especially the lungs. It allows for an increase in the radiotherapy dose to the tumor while limiting radiation delivered to healthy organs. The DHI and CI were not significantly different between the simulation techniques. The probability of pulmonary and cardiac complications is significantly lower when performed on 4DCT compared to 3DCT. However, 4DCT simulations often take a long time to delineate organs over 10 phases including OAR and tumors, take up a lot of data memory, and the X-ray tube wears out faster.

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