Dosimetric Study of Deep Learning-Guided ITV Prediction in Cone-beam CT for Lung Stereotactic Body Radiotherapy

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Purpose: The purpose of this study was to evaluate the accuracy of a lung stereotactic body radiotherapy (SBRT) treatment plan with the target of a newly predicted internal target volume (ITVpredict) and the feasibility of its clinical application. ITVpredict was automatically generated by our in-house deep learning model according to the cone-beam CT (CBCT) image database.

Method: A retrospective study of 45 patients who underwent SBRT was involved, and Mask R-CNN based algorithm model helped to predict the internal target volume (ITV) using the CBCT image database. The geometric accuracy of ITVpredict was verified by the Dice Similarity Coefficient (DSC), 3D Motion Range (R3D), Relative Volume Index (RVI), and Hausdorff Distance (HD). The PTVpredict was generated by ITVpredict, which was registered and then projected on free-breath CT (FBCT) images. The PTVFBCT was marginated from the GTV on FBCT images gross tumor volume on free-breath CT (GTVFBCT). Treatment plans with the target of Predict planning target volume on CBCT images (PTVpredict) and planning target volume on free-breath CT (PTVFBCT) were respectively re-established, and the dosimetric parameters included the ratio of the volume of patients receiving at least the prescribed dose to the volume of PTV (R100%), the ratio of the volume of patients receiving at least 50% of the prescribed dose to the volume of PTV in the Radiation Therapy Oncology Group (RTOG) 0813 Trial (R50%), Gradient Index (GI), and the maximum dose 2 cm from the PTV (D2cm), which were evaluated via Plan4DCT, plan which based on PTVpredict (Planpredict), and plan which based on PTVFBCT (PlanFBCT).

Result: The geometric results showed that there existed a good correlation between ITVpredict and ITV on the 4-dimensional CT [ITV4DCT; DSC= 0.83 ±0.18]. However, the average volume of ITVpredict was 10% less than that of ITV4DCT (p = 0.333). No significant difference in dose coverage was found in V100% for the ITV with 99.98 ± 0.04% in the ITV4DCT vs. 97.56 ± 4.71% in the ITVpredict (p = 0.162). Dosimetry parameters of PTV, including R100%, R50%, GI and D2cm showed no statistically significant difference between each plan (p > 0.05).
**INTRODUCTION**

For patients with early-stage lung cancer, stereotactic body radiotherapy (SBRT) has become one of the primary treatment options. It has been proven to significantly improve the tumor control and overall survival rate of patients with early-stage lung cancer (1–4).

Currently, the most popular treatment method is to use four-dimensional CT (4DCT) imaging to generate the internal target volume (ITV) contour, which expresses the volume of a tumor moving throughout a patient's breathing. This ITV contour from a four-dimensional averaged (4DAVG) image is used to generate a radiation treatment plan (5).

With the 4DCT technique, image acquisition is associated with the patient's breathing curve. The limitations of 4DCT are as follows: (1) Required high patient compliance as an irregular breathing curve can reduce the image quality and affect the accuracy of tumor contouring (6); (2) Complicated and professional operation as it requires a longer time to acquire 4DCT images, which could increase the instability and randomness of the simulation (7); (3) Low popularity as it is estimated that less than half of radiotherapy centers are equipped with four-dimensional scanners (8). Overall, these limits may potentially reduce the SBRT accuracy in treatment.

Conversely, CBCT has high popularity and is conventionally equipped in a linear accelerator (9). In addition, it is mainly used to compare the anatomical landmarks from treatment planning CT images in clinical practice, which are used to determine intra/inter-fraction motion (10). CBCT rotates 360° around the patient's body and then finishes the CT image scanning within a period of time (~1 min) which includes 10–12 respiration time phases and the motion trajectory of the tumor. The limitations of CBCT are as follows. First, poor image quality is the main factor affecting radiation oncologist determination of lung tumor volume (11). Second, due to a prominent amount of and artifacts, the dose calculation based on CBCT images may be inaccurate for treatment planning (12).

In recent years, “deep learning” has been extensively used in medical image processing. Among them, convolutional neural networks (CNNs) are the primary methods of target detection and segmentation (13–16). Mask R-CNN is a simple, flexible, commonly used framework for object instance segmentation, and is popular in medical image processing (17). Bouget et al. used the detection of mediastinal lymph nodes in CT images for lung cancer staging while enabling good instance detection (18). Zhang et al. successfully used Mask R-CNN to detect lung tumors on PET images, which has more effectively and precisely while suitably avoiding incorrect detection of tumors (19). Some previous studies used Mask R-CNN on segmentation, such as detection and classification the breast tumors on sonograms (20) and brain tumor segmentation for dynamic susceptibility contrast-enhanced perfusion imaging (21). These studies also show the great potential of Mask R-CNN in object detection and segmentation, presenting a possibility of it being used in clinical applications of medical images in the future.

Our preliminary research confirmed that the upgraded Mask R-CNN model could predict the ITV with CBCT image accuracy (22). Meanwhile, SBRT delivers high radiation doses to the tumor target in a hypo-fractionated area with a minimum dose to the tissue around the target area (19). Therefore, dosmetric research for lung SBRT is important. This study aimed to evaluate the dose accuracy of a lung SBRT treatment plan with ITV\textsubscript{predict} and the feasibility of its clinical application.

**MATERIALS AND METHODS**

**Patient Data**

Forty-five lung cancer patients (average age was 68 years, range: 55–86 years) who underwent SBRT at Huadong Hospital from January 2020 to July 2021 were randomly selected for this study.

**Image Acquisition**

Each patient's free-breath CT (FBCT) was scanned by a Siemens Somatom Definition AS® CT scanner (Siemens Somatom Sensation, Munich, Germany) with a pitch of 1.5 and slice thickness of 1 mm. 4DCT images were acquired with the additional assistance of Varian real-time position management (RPM) (Varian Medical Systems, Palo Alto, USA) using the same scanning parameters. The first treatment fraction of CBCT images were acquired in our CBCT system (100 kVp and 100 mAs, rotated at 360° with a speed of 6° per second), equipped with a VarianVitalBeam™ linear accelerator (Varian Medical Systems, Palo Alto, USA).

**ITV Acquisition**

The gross tumor volume (GTV) on FBCT images (GTV\textsubscript{FBCT}) and the ITV on 4DAVG (ITV\textsubscript{4DCT}) images were contoured by two radiation oncologists with expertise in lung tumors. Our model, using the Mask R-CNN algorithm with a convolutional block attention module (CBAM) module embedded, was used to automatically establish a newly predicted ITV (ITV\textsubscript{predict})

**Conclusion:** Dosimetric parameters of Plan\textsubscript{predict} are clinically comparable to those of the original Plan\textsubscript{4DCT}. This study confirmed that the treatment plan based on ITV\textsubscript{predict} produced by our model could automatically meet clinical requirements. Thus, for patients undergoing lung SBRT, the model has great potential for using CBCT images for ITV contouring which can be used in treatment planning.

**Keywords:** 4DCT, CBCT (cone beam computed tomography), SBRT (stereotactic body radiation therapy), deep learning, Mask R-CNN
FIGURE 1 | Overview of the Mask R-CNN workflow. There are two steps. First, it generates proposals for lung tumor regions based on the input cone-beam CT (CBCT) image. Second, it generates a tumor pixel-level mask based on the proposal created in the first step.

FIGURE 2 | Volumetric-modulated arc therapy (VMAT) plans with a full arc.

using the CBCT image database. Then, we registered the CBCT image and FBCT image and projected the ITV predict on the FBCT image to calculate the dose. The model workflow is shown in Figure 1.

Treatment Plan

PTV_{4DC} and PTV_{predict} were defined as ITV margins of 5 mm on 4DADV images and FBCT images, respectively. PTV_{FBCT} was defined as GTV_{FBCT} with a margin of 10 mm in the craniocaudal (CC) direction and 5 mm in the left-right (LR) and anterior-posterior (AP) directions in the FBCT image.

All patient plans were replanned in the Varian Eclipse® system (version 15.5), which was generated by a full arc and was used depending on the location and anatomic relationships of the tumors and normal tissues (Figure 2), by our experienced medical physicists. We used a 6 MV-FFF (DR: 1400 MU/min) energy and the anisotropic analytical dose calculation algorithm (AAA) with a 2.5 mm³ calculating grid in all plans. All patients received prescription of 60 grays (Gy) in 10 fractions (6 Gy per fraction) for over 2 weeks. The planning objectives aimed to cover the PTV with 95% of the prescribed dose in all plans.

Geometry Evaluation Parameters for the Prediction Model

The Dice Similarity Coefficient (DSC), 3D Motion Range (R_{3D}), Relative Volume Index (RVI), and Hausdorff Distance (HD) were calculated to assess the agreement between ITV_{predict} and ITV_{4DC}. All statistical tests were performed using SciPy in Python.

PTV Evaluation Parameters

The volume of PTV (V_{PTV}, cm³), mean dose (D_{mean}), the maximum dose received by 2% (D_{2%}), and the minimum dose received by 98% of the evaluated PTV volume (D_{98%}) were determined. The percent of the PTV receiving 100% of the prescription dose (V_{100%}) and the dose covering 95% of PTV (D_{95%}) were also calculated.

A steep dose gradient at the margin of the target volume is an important part of the SBRT plan to protect the normal organization. Some parameters for quantification have been reported in the literature, including R_{100%}, R_{50%}, the
Gradient Index (GI), and the maximum dose 2 cm from the PTV ($D_{2\text{cm}}$).

$R_{100\%}$

$R_{100\%}$ is the ratio of the volume of patients receiving at least the prescribed dose to the volume of PTV (9). When the value of $R_{100\%}$ is closer to 1, it means that the dose distribution has more conformity for PTV.

$$R_{100\%} = \frac{V_{100\%}}{V_{PTV}}$$

**TABLE 1** | Planning objectives for critical structures.

| Objectives     | Parameters | Limit     |
|----------------|------------|-----------|
| Normal Lung    | $V_{20\text{Gy}}$ | $<10\%$  |
|                | $V_{12.5\text{Gy}}$ | $<15\%$  |
| Heart          | $D_{\text{max}}$ | $<32.5\text{Gy}$ |
| Trachea        | $D_{\text{max}}$ | $<32.0\text{Gy}$ |
| Esophagus      | $D_{\text{max}}$ | $<35.0\text{Gy}$ |
| Spinal Cord    | $D_{\text{max}}$ | $<25.0\text{Gy}$ |

$R_{50\%}$ was defined as the ratio of the volume of patients receiving at least 50% of the prescribed dose to the volume of PTV in the Radiation Therapy Oncology Group (RTOG) 0813 Trial (9). The $R_{50\%}$ is an evaluation index for damage to irradiated normal tissues (24).

$$R_{50\%} = \frac{V_{50\%}}{V_{PTV}}$$

**Gradient Index (GI)**

The Gradient Index (GI) is defined as the ratio of the volume of the patient receiving at least 50% of the prescription dose to the volume of the patient receiving at least 100% of the prescription dose (25). It was used to measure dose fall-off outside of the PTV. The dose falling off outside the target volume is very important in SBRT, especially as a predictor of complications (26).

$$\text{Gradient Index (GI)} = \frac{V_{50\%}}{V_{100\%}}$$

**OARs Evaluation Parameters and Treatment Efficiency Parameters**

The dosimetric parameter acceptance of normal tissues, which refers to the RTOG 0813 Trial, is listed in Table 1. The ITV acquisition time was manually recorded for delineation efficiency and automatically recorded for model, and machine monitor units (Mus) were recorded for treatment efficiency.

**Statistical Analysis**

The statistical significance of the difference between the groups was assessed using 1-way analysis of variance (ANOVA) by SPSS software release 20.0, and the statistical significance was $p < 0.05$.

**RESULTS**

**Clinical Characteristics**

Patient and tumor characteristics of the 45 patients are described in Table 2.

**TABLE 3** | Geometry parameters of the patients.

| Parameters     | DSC  | $R_{3D}$ | RVI  | HD     |
|----------------|------|----------|------|--------|
|                | (mean ± SD) | (mean ± SD) | (mean ± SD) | (mean ± SD) |
|                | 0.83 ± 0.18 | 3.08 ± 2.81 | 1.14 ± 0.21 | 19.77 ± 21.59 |

**FIGURE 3** | Comparison of contours between ITV on the 4-dimensional CT (ITV_{4DCT}, red) and ITV prediction (ITV_{predict}, blue) in different views of patient images.
The DSC value between ITV_{4DCT} and ITV_{predict} was 0.83 ± 0.18. The DSC value indicates that ITV_{4DCT} and ITV_{predict} have a good correlation (Table 3). In addition, Figure 3 shows a visual evaluation from different perspectives. ITV_{predict} can outline the patient’s tumor contour and is similar to the radiation oncologist contouring (ITV_{4DCT}). The visual assessment shows that the results are reasonable.

**Geometry Evaluation**

The average volumes of the ITV_{4DCT} and ITV_{predict} were 21.41 ± 9.38 cm³ and 19.31 ± 8.83 cm³, respectively. Compared to ITV_{4DCT}, ITV_{predict} reduced ITV volume by 10% on average (p = 0.333). No significant difference was found in ITV volume. However, no significant difference was found in V_{100%} for the ITV with 99.98 ± 0.04% in ITV_{4DCT} vs. 97.56 ± 4.71% in ITV_{predict} (p = 0.162) (Table 4).

**ITV Evaluation**

The PTV evaluation parameters are shown in Table 5. The GI value of Plan_{predict} (GI = 3.98 ± 0.42) was slightly lower than that of Plan_{FBCT} (GI = 4.74 ± 1.01), indicating that the descending gradient of PTV was better than that of Plan_{FBCT} and second to that of Plan_{4DCT} (GI = 3.31 ± 0.89). The R_{100%} value for Plan_{4DCT} (R_{100%} = 1.05 ± 0.11) was always lower than that for Plan_{predict} (R_{100%} = 1.08 ± 0.05) and Plan_{FBCT} (R_{100%} = 1.12 ± 0.06), and the results show that Plan_{4DCT} has the best performance and high conformability. However, there was no statistically significant difference between the plans (F = 0.141).

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| Variables | Plan_{4DCT} (mean ± SD) | Plan_{predict} (mean ± SD) | Plan_{FBCT} (mean ± SD) | F | P |
|-----------|-------------------------|-----------------------------|--------------------------|---|---|
| **PTV**   |                         |                             |                          |   |   |
| Volume (cm³) | 48.81 ± 38.99          | 44.84 ± 31.93              | 43.89 ± 34.05           | 0.051 | 0.952 |
| D_{95%} (Gy) | 45.54 ± 10.72           | 51.01 ± 6.84               | 50.88 ± 4.33            | 0.384 | 0.685 |
| D_{2} (Gy)  | 77.21 ± 7.03            | 78.4 ± 14.89               | 81.93 ± 12.37           | 1.430 | 0.259 |
| V_{100%} (%)| 94.40 ± 1.80            | 94.9 ± 0.28                | 94.9 ± 0.25             | 0.931 | 0.408 |
| D_{50%} (Gy)| 59.76 ± 5.76            | 59.98 ± 3.62               | 59.59 ± 7.82            | 0.662 | 0.525 |
| R_{100%}   | 1.05 ± 0.11             | 1.08 ± 0.05                | 1.12 ± 0.06             | 0.141 | 0.872 |
| R_{90%}    | 3.48 ± 0.82             | 5.25 ± 2.01                | 4.45 ± 0.70             | 0.560 | 0.598 |
| GI         | 3.31 ± 0.89             | 3.98 ± 0.42                | 4.74 ± 1.01             | 0.573 | 0.592 |
| D_{2cm} (Gy)| 30.27 ± 4.39            | 31.18 ± 3.46               | 33.46 ± 2.24            | 0.070 | 0.933 |
| **OARs**   |                         |                             |                          |   |   |
| Lung       | 5.83 ± 1.48             | 5.30 ± 0.85                | 5.50 ± 0.99             | 0.420 | 0.690 |
| V20 (%)    | 3.05 ± 0.92             | 2.58 ± 0.71                | 2.80 ± 0.57             | 0.820 | 0.520 |
| Heart      | 11.15 ± 6.58            | 9.84 ± 5.89                | 9.91 ± 6.42             | 0.058 | 0.994 |
| Trachea    | 0.46 ± 0.04             | 0.55 ± 0.07                | 0.58 ± 0.06             | 0.681 | 0.791 |
| Esophagus  | 9.14 ± 3.42             | 8.43 ± 2.14                | 7.01 ± 2.61             | 0.457 | 0.647 |
| Spinal Cord| 9.57 ± 2.61             | 8.89 ± 0.01                | 6.70 ± 2.45             | 0.926 | 0.431 |
| **Treatment efficiency parameters** | | | | | |
| Generate ITV time (min) | 30.28 ± 3.74 | 1.45 ± 0.31 | 24.13 ± 4.93 | 756 | 0.000* |
| MU         | 1.023 ± 0.83           | 1.059 ± 0.028             | 1.042 ± 0.123           | 0.837 | 0.713 |

*A significant difference existed (p < 0.05). SD, standard deviation.
The contouring in different views is also similar for the PTV of each plan (Figure 4). The visual assessment shows that the results are reasonable. Figures 5, 6 show the dose color wash and the dose volume histogram (DVH) of the patients, which were calculated for each plan.

OARs and Treatment Efficiency Evaluation
The estimated dosimetric parameters for all plans met the criteria specified in the RTOG 0813 protocol. The results show that the V20 of Plan\textsubscript{predict} was better than that of Plan\textsubscript{4DCT} (with a reduction of 15.4%) and Plan\textsubscript{FBCT} (with a reduction of 7.8%), which obviously protected the lung (Figure 7), but no difference existed in the dosimetric parameters. Additionally, there was no statistically significant difference in each plan with the maximum dose (D\textsubscript{max}) for the heart, esophagus, and spinal cord (Table 4).

The average times of generating ITVs were 1.45 ± 0.31 and 30.28 ± 3.74 min for automatic (by model) and manual ITVs, respectively. The model helped reduce it by 95% of the time on average ($p = 0.000$).

DISCUSSION

Geometrical Accuracy of the Prediction Model
We used geometric parameters to evaluate the similarity between ITV\textsubscript{4DCT} and ITV\textsubscript{predict}. The DSC value was 0.83 ± 0.18, showing good agreement between the ITV\textsubscript{predict} and ITV\textsubscript{4DCT} contour. DSC > 0.7 is considered to be in good agreement with the gold standard (28, 29). This result can become the basis for follow-up research as it confirmed the feasibility of CBCT images to predict ITV. The accuracy of the ITV contours will directly affect the optimization and calculation of the DVH plan (30). The results show that the ITV\textsubscript{predict} volume is 10% smaller than the ITV\textsubscript{4DCT} volume. Dou et al. found that 4DCT images should be used with caution for patients with highly irregular breathing. The simulation indicates that low-pitch helical 4DCT processes potentially yield large tumor motion measurement errors and overestimate tumor motion (31). However, there was no significant difference between ITV\textsubscript{4DCT} and ITV\textsubscript{predict}. This result of ITV\textsubscript{predict} volume reduction was acceptable.
4DCT Limitation and CBCT Potential Application

Four dimensional CT (4DCT) was acquired during the patient positioning stage and could not reflect the deviation of the tumor's respiratory movement during treatment (32, 33). Rabinowitz et al. showed that during the patient positioning stage and the treatment stage, the tumor deviation caused by respiratory motion was an average of 5.1 mm. For thoracic tumors, the tumor deviation caused by respiratory motion could reach 5.8 mm (34). Yang et al. showed that 4DCT could only collect signals of a limited number of respiratory phases, but the patient's breathing may change at any time and cannot accurately reflect the patient's tumor movement during treatment (35). The study showed that CBCT and maximum intensity projection (MIP) images are equivalent in determining the location of ITV (36). Li et al. showed that 4DCT and CBCT images can indicate variations and inter-fractional setup displacement (37). In our study, we used the first CBCT image at the time of treatment to show the respiratory motion range of a tumor during treatment.

PTV Evaluation

Compared with conventional treatment, SBRT has higher requirements for the PTV dose gradient and limited dose limitation of organ at risks (OARs). The RTOG0813 protocol (26) provides guidance on the acceptable values of \( R_{100\%} \), \( R_{50\%} \), and \( D_{2cm} \) based on the PTV volume. The values of \( R_{100\%} \) and \( R_{50\%} \) in Plan_{4DCT} and Plan_{predict} were 1.05 ± 0.11, 1.08 ± 0.05, 3.48 ± 0.82, and 5.25 ± 2.01 respectively, which were comparable but slightly different. The result of \( R_{100\%} \) indicated that Plan_{predict} and Plan_{4DCT} have a similar dose coverage for PTV. The \( R_{50\%} \) value of Plan_{predict} increased by nearly 30% compared with that of Plan_{4DCT}, which shows that Plan_{4DCT} has a stronger ability to constrain PTV. All plans meet the RTOG0813 protocol and can be used in clinical practice.

In our study, we also researched the dosimetry of GTV on FBCT images to generate Plan_{FBCT}. The results show that after the RTOG0813 guide on margin from GTV, it can also meet the treatment standards and hence can be used for treatment planning. Tian et al. (38) compared the treatment planning and dose calculation of average intensity projection (AIP) and FBCT for SBRT and concluded that the dosimetric of the two datasets were similar.

OARs Evaluation

In addition, the RTOG 0813 agreement contains restrictions on each OAR, such as the lung and spinal cord. For SBRT patients, high-energy rays inevitably pass through a part of normal lung tissue, which affects lung function. Jin et al. (39) found that when V20 was >25%, the incidence of radiation pneumonia significantly increased. Our results show that the mean values of V20 in Plan_{4DCT} and Plan_{predict} were 3.05 ± 0.92% and 2.58 ± 0.71%, respectively, indicating that Plan_{predict} reduces the volume of radiation received by normal lung tissue, thereby reducing the incidence of radiation pneumonitis. The thoracic spinal cord is...
more likely to be injured in patients with lung SBRT. Radiation myelitis may cause serious consequences, such as paraplegia and respiratory paralysis. The values of spinal cord $D_{\text{max}}$ in the Plan$_{4DCT}$ and the Plan$_{\text{predict}}$ are 9.57 ± 2.61 Gy and 8.89 ± 0.01 Gy. This shows that Plan$_{\text{predict}}$ reduces the maximum dose received in the spinal cord, which can thus reduce the incidence of radiation myelitis.

### Treatment Efficiency Evaluation

Currently, the model predicts the ITV volume of large tumors more accurately. For patients with lung SBRT, this model can generate ITV on CBCT images in, on average, 1.45 ± 0.31 min. In our research, the generated ITV time of Plan$_{\text{predict}}$ was significantly reduced by nearly 95% compared with that of Plan$_{4DCT}$. Hence, Using the model to input CBCT images can greatly shorten the time to collect patient images and significantly increase the efficiency of tumor delineation for physicians.

This study has some limitations. Firstly, the number of patient samples included was small. Therefore, our patient data did not represent the whole spectrum. Tumors of different sizes and different locations should be included in the future. This could increase patient data for a more uniform tumor volume distribution to ensure accuracy of results in the future.

### CONCLUSION

Geometric results show that self-generated ITV$_{\text{predict}}$ has a good correlation with ITV$_{4DCT}$, although the ITV$_{\text{predict}}$ volume is 10% smaller than the ITV$_{4DCT}$ volume. This work confirmed the feasibility of the clinical application of ITV$_{\text{predict}}$ to make a treatment plan. There were no significant dosimetry differences between Plan$_{4DCT}$ and Plan$_{\text{predict}}$. Thus, our model has potential application in institutions with or without 4DCT scanning technology or when patient breathing is irregular.

### DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

### ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

### AUTHOR CONTRIBUTIONS

SZ and BL: conception and design. XZ and YL: acquisition of data. WG, LZ, and FM: analysis of data. SJ, BL, and JQ: writing, review and/or revision of the manuscript. All authors reviewed, read, and approved the final manuscript and authors contributed to the article, and approved the submitted version.

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