Volume 20, No 2 | International Journal of Radiation Research, April 2022

Do auto-planning intensity modulated radiotherapy treatment plans for central lung cancer have improved quality over manual plans?

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► ***Original article***

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Received: March 2021
Final revised: July 2021
Accepted: August 2021

Int. J. Radiat. Res., April 2022; 20(2): 499-505

DOI: 10.52547/ijrr.20.2.35

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Keywords: *Pinnacle auto-planning, IMRT, lung cancer.*

ABSTRACT

Background: To investigate the performance of Auto-Planning intensity modulated radiation therapy (IMRT) plans for patients with central lung cancer and to determine whether Auto-Planning improves the quality of IMRT plans. ***Materials and Methods***: Thirty patients treated with IMRT for central lung cancer were replanned with the Pinnacle[3] Auto-Planning module. The dose distribution at the target, organ at risk (OAR) sparing, dose falloff in the five rings outside of target, monitor units (MUs), planning time, and dosimetric verification in terms of the γ passing rate were evaluated. A Wilcoxon signed-rank test was performed to assess differences between groups ($p<0.05$). ***Results***: The target homogeneity in the Auto-Planning were significantly better than that in the manual plans, the target conformity in both groups were similar. The Auto-Planning plans yielded lower V_5, V_{10}, V_{13}, V_{20}, V_{30}, V_{40} values, mean lung dose of total lung ($p<0.01$), and D_{max} of spinal cord ($p<0.01$) and V_{30} of heart ($p<0.01$). No significant difference was found for the V_{40} of the heart ($p=0.203$). The Auto-Planning module reduced the D_{mean}, D_2 and D_5 values in all rings outside of PTV. The planning time was 52.5% shorter for Auto-Planning plans than for manual plans ($p<0.01$), and 4.4% additional MUs were required with Auto-Planning. No difference was observed for the γ passing rate. ***Conclusion***: Auto-Planning for central lung cancer could improve homogeneity of target volumes, significantly delivery lower dose to OARs and steeper dose falloff outside of tumors while reducing the planning time.

INTRODUCTION

Intensity modulated radiation therapy (IMRT) has become an important radiotherapy technique in the treatment of lung cancer. Multiple manual steps are involved during the design of IMRT: optimization of the objective, criteria and cycles must be manually adjusted. Therefore, the quality of the plans mainly depends on the experience of the dosimetrist, who is responsible for the above adjustments. In addition, manual plan development is time consuming, and the plan designers need much training in order to prevent long-term problems in radiation therapy.

To reduce individual differences caused by manual planning and to improve overall planning quality, many automatic algorithms have been introduced. Two typical automatic planning approaches have been developed [1-26]. The first approach, called knowledge-based planning, [2, 3, 8, 11, 12 ,22, 23], utilizes similar cases for model training and dosimetric testing; it is very important to compile a sufficient number of high-quality plans to build a predictive model. The other approach is the use of an Auto-Planning module, [4-7, 10, 16-19, 21, 25], which implements dynamic procedures during optimization, where constraints and objectives are continuously adapted based on iterative algorithms.

The use of an Auto-Planning module has been reported in studies for head and neck cancer, [4-6, 10, 16] breast cancer, [8, 17] non-small-cell lung cancer, [18] liver cancer, [21] whole brain cancer with hippocampal sparing, [25] spinal metastases, [26] and prostate cancer [7, 19, 20] it have demonstrated that Auto-Planning plans have similar or better target coverage than manual plans and significant reduction in the dose delivered to the organs at risk (OARs). Although Auto-Planning plans have been previously compared to manual plans for various types of cancer, it remains unclear whether Auto-Planning can also generate better plan quality than manual planning for central lung cancer, given the different anatomical complexities because the lungs and the

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[DOI: 10.52547/ijrr.20.2.35]

above described regions.

This study aims to evaluate the characteristics and effectiveness of Auto-Planning for IMRT treatment of central lung cancer. The dosimetric differences in target volume and OARs, dose falloff outside of tumor, the planning time, monitor units (MUs), dosimetric deliverability were evaluated by comparing with manual plans. To our knowledge, there have been no reported studies of automated compared with manual plans for central lung cancer. The results of this article will contribute to the clinical application of automatic planning for central lung cancer.

METHODS AND MATERIALS

Patient information

To minimize the impact of different tumor anatomical locations on Auto-Planning, 30 histologically or cytologically confirmed central lung cancer patients treated in this department from May 2016 to December 2016 were selected. Patient information is shown in table 1. This study was approved by the Native Ethics Committee (approval No. KS1974) on February 22, 2019. The total dose was prescribed as 60 Gy delivered in 30 fractions to the planning target volume (PTV) and to 95% of the PTV to reach the prescription dose.

Table 1. Patient demographics.

	Total
Age(years)	
Median	61
Range	41-86
Sex(no. of patients)	
Male	29
Female	1
Disease Stage	
II	20
III	10
Disease Site	
Right	15
Left	15
PTV Length (cm)	
Mean	9.8
Range	7-17.3
PTV Width (cm)	
Mean	9.5
Range	5.6-12.8
PTV Volume (cm^3)	
Mean	280.6
Range	118.9-451.3

Definition of target volume, OARs and dose prescription

The target volumes and OARs were delineated manually by an experienced radiation oncologist. The gross tumor volume (GTV) was the visible tumor focus outlined on a CT image using the MX4000 CT Scanner System (Philips Medical Systems, Shenyang, China) in accordance with the pathological structure. The clinical target volume (CTV) typically encompassed the GTV with an additional 5-8 mm margin. The PTV was created by further extending a 3 -4 mm margin from the CTV to account for respiratory motion and setup uncertainties, and could be changed appropriately according to the actual anatomical location of the patient's tumor. The OARs included the total lungs (the right lung plus the left lung minus the intrapulmonary GTV), the spinal cord and heart. Treatment planning was performed according to the following clinical objectives: V_{20} (i.e., percentage of the total lung volume receiving ≥20 Gy) ≤ 25%, mean lung dose (MLD) ≤13 Gy for the total lungs, D_{max} (the maximum dose of spinal cord) <45 Gy for the spinal cord, and D_{mean} <26 Gy, V_{30} (i.e., percentage of the heart volume receiving ≥30 Gy) < 40%, and V_{40} (i.e., percentage of the heart volume receiving ≥40 Gy) <30% for the heart.

Manual planning and optimizing

For each patient, a manual (Manu) plan and an automatic (Auto) plan were created and compared. All plans were generated for a Varian Edge linear accelerator (Varian Medical Systems, Palo Alto, CA, USA) with 6 MV imaging on a Pinnacle^3 v9.10 treatment planning system (Philips Radiation Oncology, Madison, WI). The dose optimization algorithm for all plans in the Pinnacle^3 planning system (Fitchburg, MA, USA) used direct machine parameter optimization. The maximum number of all segments and maximum iterations and were 60 and 50, respectively, for the plan optimization, and the maximum MUs and segment area were 4 and 4 cm^2, respectively. The grid resolution was 2 mm.

All patients were treated with an IMRT plan. For each Manu plan, depending on the location of the tumor in relation to the patient's anatomy, 4 or 5 coplanar beams were used. In the manual clinical plans, it was different to satisfy the ideal constraints for the PTV or at least one OAR; minor deviations were accepted by the approving physician only if the ideal constraints could be achieved for the OARs and if the maximum dose remained within the GTV. All clinically accepted and delivered treatment plans were used as the reference plans in this study.

Auto-planning

To analyze the differences between the automated and manual plans, the Auto plans for each patient were created by a dosimetrist with more than 8 years of experience. For each Auto plan, the same geometry was maintained as in the corresponding manual plan. To best meet the planning goals, the Auto-Planning module required the use of a template of configurable parameters to iteratively adjust the IMRT planning parameters. This template included the prescription, treatment technique and machine, beam parameters, and automated planning settings, which was generated based on the data from an additional 16 patients with central lung cancer. For the OARs, the

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Auto-Planning clinical objectives option in the Pinnacle[3] device included Max DVH, Mean Dose and Max Dose. For every clinical objective there are four priority levels: Low, Medium, High and Constrain. The Auto-Planning module met the OARs goals according to priority levels. Details of the Auto plan OAR optimization goals are listed in table 2.

Table 2. Auto plans OAR optimization goals.

Organ at risk	Objective	Dose level		Priority	Compromise
Spinal Cord	Max Dose	4400 cGy		High	No
Total Lung	Max DVH	500 cGy	30%	Medium	Yes
Total Lung	Max DVH	2000 cGy	18%	Medium	Yes
Total Lung	Max DVH	3000 cGy	8%	Medium	Yes
Heart	Max DVH	3000 cGy	35%	Medium	Yes
Heart	Max DVH	4000 cGy	25%	Medium	Yes

To create high-quality plans, the Auto-Planning module generated not only multiple regions of interest out of the target volume to meet the dose requirement in the target volume but also multiple additional risks of interest (ROIs) out of the OARs to reduce OAR doses during the optimization process. These special ROIs were very difficult to manually create for all manual plans. In theory, quantitatively better plans could be generated by the Auto-Planning module relative to those generated by manual planning. If needed clinically, the Auto plans could be further optimized just as any manually created plan and thus could serve as a high-quality starting point for any manual optimization.

Plan evaluation and statistical analysis

To evaluate the dose falloff outside of the target volumes, five ring structures were generated in this study. Four ring structures were delineated within the ring outside the PTV, named ring 1, ring 2, ring 3, ring 4 and ring 1 was generated by applying a 5 mm margin to the PTV in 3-dimensions. Ring 2, ring 3, ring 4 were defined as 5 mm, 10 mm and 10 mm margins in 3-dimensions relative to ring 1, ring 2, ring 3, respectively. Ring5 were defined as the body minus ring4, as shown in figure 1.

Dose volume histograms (DVHs) were calculated to evaluate the dose distributions of the target volume and the OARs. Parameters used to evaluate the target volume included the following: 1) The conformity index (CI) = $V_{T,\,ref}/V_T \times V_{T,\,ref}/V_{ref}$, where $V_{T,ref}$ is the target volume covered by the reference isodose (95% of the prescribed dose), V_T is the target volume, and V_{ref} is the volume of the reference isodose [27]. A CI closer to 1 indicates a better CI of the dose distribution; 2) The homogeneity index (HI) = $(D_2 - D_{98})/D_p$, where D_p is the prescription dose, D_2 is the corresponding dose for 2% of the target volume on the DVH, and D_{98} is the corresponding dose for 98% of the target volume [28]. A smaller HI mean a more homogenous dose distribution; and 3) D_{mean}, D_2 and D_{98}. The DVH analysis was performed for the lung, spinal cord, heart, body, ring 1a, ring 1b, ring 2a, ring 2b, ring 3a, ring 3b, ring 4a, ring 4b, ring 5a and ring 5b. The MUs and planning time were also evaluated. The effective working time required by the dosimetrist was defined as the planning time. Dosimetric verification was performed and the γ passing rate with acceptance criteria 3%, 3 mm, and local approach was evaluated to determine whether both the Auto plans and Manu plans could be reliably delivered. Each patient plan was transferred to a MatriXX (IBA dosimetry, GmbH, Germany) 2D array to delivery dose.

All statistical analyses were performed with SPSS software v20.0 (SPSS, Inc., Chicago, IL, USA), and the paired, two-sided Wilcoxon signed-rank test was used to evaluate the differences in the dose parameters between the Auto and Manu plans ($p < 0.05$).

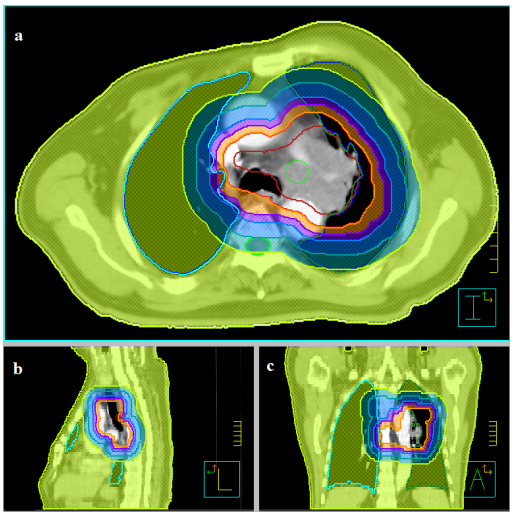


Figure 1. a: The rings outside of PTV show in coronal view; **b:** The rings outside of PTV show in sagittal view; **c:** The rings outside of PTV show in horizontal view. Ring 1: orange; ring 2: purple; ring 3: blue; ring 4: green; ring 5: yellow-green; PTV: red; GTV: dark red.

RESULTS

Dose to the target volume

The dosimetric parameters of the target volume for the Manu and Auto plans are reported in table 3. Compared with Manu plans, the D_2 and HI values of the Auto plans were lower (all $p<0.01$). HI was 0.08±0.01 for the Auto plans and 0.10±0.01 for the Manu plans, $p<0.01$. Both the D_{mean} and CI for the target volume were similar between the two plan groups ($p>0.05$). For the D_{98}, the value of the Manu plans was lower to that of the Auto plans ($p<0.01$). The irradiation dose curves and the DVH of the PTV of an example patient are shown in figure 2.

Dose to the OARs (spinal cord, heart, total lungs and body)

The comparison of the dosimetric parameters of the OARs between the Manu and Auto plans is summarized in table 4. For the total lungs, a statistically significant reduction in all dosimetric

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[DOI: 10.52547/ijrr.20.2.35]

parameters was observed for the Auto plans relative to the Manu plans ($p<0.01$). Both the Auto and Manu plans were able to maintain a D_{max} far below 45 Gy to the spinal cord of every patient, with the Auto plans achieving a D_{max} 2.52 Gy less than that achieved by the Manu plans ($p<0.01$). Similar differences were observed for the heart V_{30} ($p<0.01$). For the heart V_{40}, no significant difference was found between the Auto and Manu plans.

Table 3. Dosimetric parameters for the target volume for Manu and Auto plans.

	Manu plan	Auto plan	p value
D_{mean} (Gy)	62.79±0.4	62.75±0.43	0.455
D_2 (Gy)	64.39±0.47	63.20±0.53	<0.01
D_{98} (Gy)	58.81±0.33	59.01±0.30	<0.01
CI	0.82±0.08	0.81±0.07	0.665
HI	0.10±0.01	0.08±0.01	<0.01

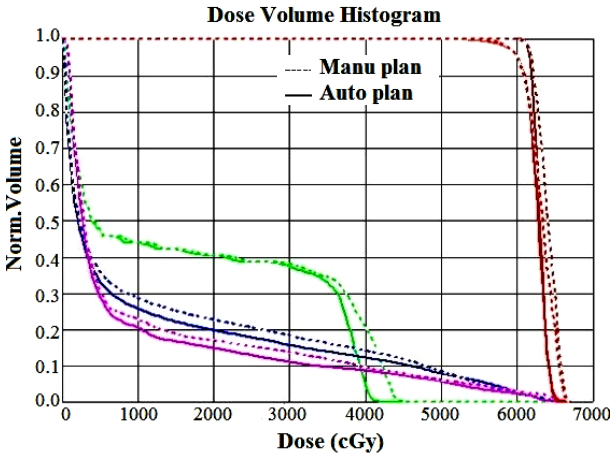


Figure 2. The comparison of DVHs for the PTV and OARs in Auto plan and Manu plan for patient 1. PTV: red. GTV: maroon. Lung: blue. Spinal cord: green. Heart: purple.

Table 4. Dosimetric parameters of OARs for Manu and Auto plans.

	Manu plan	Auto plan	p value
Total Lung			
MLD (Gy)	12.36±1.94	11.68±1.35	<0.01
V_5 (%)	39.01±6.68	37.10±5.67	<0.01
V_{10} (%)	29.62±4.77	28.11±4.56	<0.01
V_{13} (%)	26.79±4.43	24.99±5.12	<0.01
V_{15} (%)	25.25±4.35	23.94±3.36	<0.01
V_{20}(%)	22.32±4.24	20.01±4.69	<0.01
V_{30}(%)	18.06±3.89	15.82±4.01	<0.01
V_{40}(%)	13.73±3.39	12.20±1.35	<0.01
Spinal Cord			
D_{max}(Gy)	41.64±4.33	39.12±5.99	<0.01
Heart			
V_{30} (%)	27.03±12.33	25.41±7.99	<0.01
V_{40} (%)	20.42±10.69	20.14±5.94	0.203

Dose to the 3 cm annular region outside the target volume

Considering the anatomical complexity of the central lung cancers and OARs, this article evaluated the region outside the target volume. The dose to the rings are listed in table 5. For all the rings, compared with the Manu plans, the Auto plans significantly reduced the D_{mean}, D_2 and D_5, meaning that the Auto plans had steeper dose falloff outside of tumors comparing with the Manu plans.

MUs, planning time and dosimetric verification

Overall, the Auto plans required significantly more MUs (619±107) than the Manu plans (592±88). For all patients, the average planning time was 19 minutes for the Auto plans and 40 minutes for Manu plans, resulting in a 52.5% shorter planning time for the Auto plans; this difference was statistically significant ($p<0.01$), (table 6). For the γ passing rates, no statistically significant difference was observed, whose average values were > 96% for both the Auto and Manu plans.

Table 5. Dosimetric parameters comparison for the rings outside of the target volume.

	Manu plan	Auto plan	p value
Ring 1			
D_{mean} (Gy)	56.50±0.55	54.76±0.47	<0.01
D_2 (Gy)	63.42±0.73	62.98±0.71	0.016
D_5 (Gy)	62.65±0.81	62.24±0.84	0.023
Ring 2			
D_{mean} (Gy)	44.91±1.47	42.89±1.23	<0.01
D_2 (Gy)	60.3±1.18	58.21±0.99	<0.01
D_5 (Gy)	59.06±1.95	57.25±0.98	<0.01
Ring 3			
D_{mean} (Gy)	31.92±1.51	29.17±1.17	<0.01
D_2 (Gy)	55.61±1.04	53.75±1.20	<0.01
D_5 (Gy)	55.11±1.18	52.44±1.01	<0.01
Ring 4			
D_{mean} (Gy)	22.00±1.60	17.76±1.18	<0.01
D_2 (Gy)	51.96±0.89	44.01±1.11	<0.01
D_5 (Gy)	50.85±1.49	42.17±1.15	<0.01
Ring 5			
D_{mean} (Gy)	4.15±1.45	2.84±1.31	<0.01
D_2 (Gy)	40.25±0.99	37.01±1.01	<0.01
D_5 (Gy)	39.01±1.22	35.49±1.19	<0.01

Table 6. Comparison of MU and planning time.

	MA plan	AP plan	p value
MUs	592±88	619±107	0.024
Planning Time(min)	40±2.6	19±4.2	<0.01
γ passing rate (%)	96.1± 3.0	96.7 ± 2.2	0.882

Table 6. Comparison of MU and planning time.

	MA plan	AP plan	p value
MUs	592±88	612±135	0.03
Planning Time(min)	40±2.6	11±3.5	<0.01
γ passing rate (%)	96.1± 3.0	96.8 ± 2.0	0.897

DISCUSSION

In general, the stage, location and size of tumor could affect the reliability of the dosimetric results. If the patients share the same tumor stage and similar tumor primary location and tumor size, the dosimetric comparison will be more reliable. Otherwise, larger differences will produce less reliable results. All the patients in this article had stage II or III central lung cancer, with tumors located

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[DOI: 10.52547/ijrr.20.2.35]

in the left lung lobe for half of the cohort and the right lung lobe for the other half. Therefore, the results of this study may provide reliable evidence for the assessment of Auto-Planning for lung cancer.

The main purpose of this study was to investigate the effectiveness of Auto plan; therefore, we did not manually modify the Auto plans after optimization. The results of this study showed that the HI of the Auto plans was better than that of the Manu plans, while the CI was inferior. This is because no post optimization was performed for any of the Auto plans, while several manual adjustments were made to the Manu plans. This result is consistent with the results of one study [6] but inconsistent with those of a separate study.[7] In general, homogeneity competes with conformity, so it is difficult to balance the two indexes, as shown by the results in this study.

The results shown in table 4 indicate that the Auto plans protected the OARs better than the plans generated manually. To make high-quality plans, during the optimization process, the Auto-Planning module generates not only multiple regions of interest out of the target volume to meet the dose requirement in the target volume but also multiple additional ROIs out of the OARs to reduce OAR doses. The settings for the OAR optimization-objective parameters also played a role. The spinal cord is a serial organ. The primary concern is to protect this organ from receiving radiation up to 45 Gy, so the priority for the spinal cord is set to "high". Radiation pneumonitis is a major side effect of thoracic cancer radiotherapy, [29-31] and therefore the dose to the lungs should be reduced as much as possible when generating lung cancer radiotherapy plans. Three optimization objectives were established to limit the dose delivered to the lung, and the priority for the lung was set to "medium", just below the priority set for the spinal cord. Comparing to the Manu plans, the Auto plans delivered significantly reduced doses to the lungs, so the incidence of radiation pneumonitis would have been reduced. The Auto plans also significantly reduced the doses to the other OARs. Therefore, the technical parameters of the Auto-planning module can be used to protect the OARs.

The quality of the manual plans mainly depends on the experience of the dosimetrist. It is possible that a plan designer with 10 years of experience can make plans as good as or even better than those generated by the Auto-Planning module, but this process would be time consuming and likely impossible for a center with many patients. In general, the Auto-Planning module could generate clinically acceptable plans automatically without human intervention and spend less time to produce plans that meet clinical quality requirements than manual plans. The reduction in planning time means that we could quickly design multiple automatic plans for patients, allowing the radiation oncologists choose the best plan for clinical treatment.

It has been reported that Auto-Planning can reduce the dose delivered to the OARs [5-7, 16, 19-21]. However, no research has reported this information for dose falloff outside of tumors. This study was the first to evaluate the dose distribution outside of the target volume for routine clinical therapy. By comparing the rings away from the PTV, as shown in table 5, we found that the Auto plans delivered a lower mean dose, D_2 and D_5 values than the Manu plans, indicating that the dose in all the rings fell off faster for the Auto plans than for the Manu plans.

The Manu plans required fewer MUs than the Auto plans. The greater number of MUs required for the Auto plans may potentially increase the risk of secondary cancer. Dose verification was performed in our study to check that dose distributions calculated for both the Auto and Manu plans could be reliably delivered, and the results showed that the differences in these distributions were not statistically significant.

Several studies have been recently published showing that Auto-Planning has been applied to spinal metastases, [26] head and neck cancer, [4-6, 10, 16] prostate cancer, [7, 19, 20] breast cancer, [8, 17] whole brain cancer with hippocampal sparing, [25] non-small -cell lung cancer, [18] and cervical cancer [23, 24] using IMRT, volumetric modulated arc therapy or SBRT. For most of these studies, automated planning achieved improved target conformity and homogeneity indexes except for head and neck cancer, where they were worse [4, 32]. Although the results of automated planning are inconsistent in terms of target conformity and/or homogeneity, a common conclusion is that the planning time and dose delivered to OARs with automated planning were significantly reduced [5-7, 16, 19-21]. Moreover, following a blinded clinical evaluation, most of the automated plans were equivalent to or better than the manual plans and could be used in the clinic with no further optimization [4-7, 21, 26]. Naturally, the Auto-planning module has some limitations. Despite the name, Auto-planning is not fully automated, and some steps still need to be performed manually. For example, the beam arrangement and the initial optimization-objective parameters must be initially set, cannot be changed during optimization, and largely depend on the experience of the medical dosimetrist [10, 16-18, 22]. Furthermore, setting up the Auto-Planning and script templates for the first time heavily relies on experienced user input; without it, the benefit of Auto-Planning may be doubtful [10, 17, 18]. Future developments for Auto-planning modules should improve or revise these limitations to achieve fully automated planning.

CONCLUSIONS

This paper evaluated the characteristics of

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[DOI: 10.52547/ijrr.20.2.35]

Auto-Planning and manual planning for central lung cancer treatment. Our results showed that the Auto-planning module not only could speed up the planning course, but also deliver better PTV conformity, PTV homogeneity, OARs sparing and steeper dose falloff outside of tumors than manual planning. The Auto-Planning module is becoming a very valuable and important clinical tool which could reduce user variability while improving the quality and efficiency of the plans.

ACKNOWLEDGEMENTS

Not applicable.

***Availability of data and materials*:** The datasets generated during and/or analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

***Funding*:** This work was sponsored by the Interdisciplinary Program of Shanghai Jiao Tong University (Grant No. YG2019ZDB07) and Nurture projects for basic research of Shanghai Chest Hospital (Grant No. 2019YNJCM05).

***Competing interest*:** The authors declare that they have no competing interest.

***Author' contributions*:** HC analyzed the data and wrote the manuscript. All authors participated in the design of the presented study, reviewed the manuscript prior to its publication. All authors read and approved the final manuscript.

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