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Original paper

Dosimetric comparison and biological evaluation of PET- and CT-based target delineation for LA-NSCLC using auto-planning

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ABSTRACT

Using auto-planning, the dosimetric and biological differences between PET- and CT-based target delineation in LA-NSCLC were studied. Twenty-three patients with IIIA-IIIB NSCLC were included in this retrospective study. For each patient, two AP plans (Plan_PET, Plan_CT) were generated based on PET- and CT-based gross tumor volume (GTV_{PET}, GTV_{CT}). The volume, boundary and center of mass (COM) of GTVPET and GTVCT were compared. Dosimetric indicators such as mean lung dose (MLD) and so on were evaluated. Tumor control probability (TCP) of GTVPET and GTVCT and normal tissue complication probability (NTCP) of total lung and heart were calculated. A paired-samples *t*-test was used to check for significant differences ($p < 0.05$) between dataset. Volume of GTVPET was significantly smaller than that of GTVCT. Under the premise that GTVPET met the clinical requirements in Plan_PET, GTVCT couldn't satisfy the requirements. GTVCT met the clinical requirements in Plan_CT, and four cases of GTVPET could not satisfy the requirements. Compared with Plan_CT, Plan_PET significantly reduced MLD, V5, V10, V13, V15, V20, V30 and V40 of total lung, and MHD, V30 and V40 of heart, and MUs. No significant difference was observed with respect to Dmax of spinal cord. TCP of GTVPET in Plan_PET was significantly higher than that of GTVCT. NTCP of total lung in Plan_PET was significantly lower than that in Plan_CT. There were differences in volume, boundary, and COM of targets based on the two delineation methods. These led to differences in dosimetric and biological indicators. For LA-NSCLC, the way that most hospitals only use CT to delineate the target should be careful consideration.

1. Introduction

Lung cancer is the most prevalent malignancies and the leading cause of cancer death worldwide [1]. More than 80% of lung cancer is non-small cell lung cancer (NSCLC) [2], of which 30%–40% of NSCLC belongs to local advanced stage which is not suitable for surgical resection. Usually, radiotherapy combined with chemotherapy is the standard treatment for these patients [3].

At present, the targets are mainly delineated on CT images in intensity modulated radiotherapy (IMRT) for lung cancer patients. However, with the development of technology, PET/CT combined imaging can simultaneously collect PET and CT data in one scan [4]. In addition to providing accurate anatomical images, PET/CT also provides functional metabolic images of tissues. It has the potential to break through from physical IMRT to biological IMRT. PET/CT has become the preferred diagnostic mode for patients with cancer [5]. Therefore, it is increasingly used for target delineation in radiotherapy treatment planning [6].

Currently, there are two main types of commercial automatic planning that have been developed. One is the knowledge-based treatment planning (KBP) module developed by Varian [7]. And the other one is the auto-planning (AP) module based on progressive automatic optimization algorithm developed by Philips [8–10]. The AP module was used in this study. It is a fully integrated module in the treatment planning system (TPS). During AP, individual optimization goals, constraints and weights are automatically added and adjusted. The optimizer is also automatically run multiple times with adjustments being made during and between optimization runs [11]. AP effectively improves the efficiency of the treatment planning design, reduces the time required for treatment planning. And the most important thing is that it can ensure the consistency of planning quality and remove inter and intra planner variation. A study [12] showed that AP significantly reduced the inter-planner variation compared to manual planning (MP).

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Some researches [13–16] had reported differences in tumor size between PET- and CT-based delineation methods. Prathipati et al. [15] found that PET/CT-based contours more accurately delineates tumour volumes (obstructive pneumonia and atelectasis), decreases contouring variability through more accurate tumour margins identification, and detects new lymph node volumes. Cheebsumon et al. [16] compared the pathological results with the PET- and CT-based targets, respectively. They found that the maximum diameter derived from CT-based targets was overestimated compared to pathology, whereas the PET-based targets were closer to pathological results. The dosimetric differences of targets using two delineation methods had also been reported by some studies [17–19]. However, these studies all used MP, which varied greatly among different planners, and the tumor staging span was large. In addition, as far as we know, most studies have compared dosimetric differences. So, performing biological evaluation by calculating TCP and NTCP becomes more and more important. In this subject, we studied the differences in dosimetry and biology between PET- and CT-based targets in LA-NSCLC using AP.

In this study, targets of LA-NSCLC were delineated based on PET and CT respectively, and the plans were generated using AP. This paper studied the differences between targets delineated by the above two methods in the following three aspects. Firstly, the differences of volume, boundary and center of mass of target were studied. Secondly, the dosimetric differences of target and OARs were studied. Thirdly, the biological differences of TCP of targets and NTCP of OARs were studied. AP was used to avoid the individual differences in different planners, which was conducive to evaluate the dosimetry and biological differences between targets and OARs based on the two delineation methods. We expect to provide dosimetric and biological specific data references when clinicians use different methods to delineate the LA-NSCLC target.

2. Materials and methods

2.1. Patient selection

From January 2017 to August 2018, 23 patients with locally advanced IIIA-IIIB non-small cell lung cancer were included in this retrospective study. All patients could not undergo radical surgery after discussion by surgeons and radiotherapists. The median age of the patients was 61 years old (range, 38-81y). The study was approved by the ethics committee and all patients signed informed consent. The general clinical characteristics of patients were shown in Table 1.

2.2. Imaging

All patients were immobilized in the supine position, with their arms above their heads. CT scans were performed using the MX4000 CT Scanner System (Philips Medical Systems) under free breathing conditions. Images were taken at a 3 mm thickness throughout the upper edge of the second cervical vertebra to the lower edge of the second lumbar vertebra. ^{18}F-FDG PET/CT was performed using Biography mCT-sPET/CT (Siemens Healthcare, Erlangen, Germany). All Patients fasted more than 6 h and ^{18}F-FDG was injected intravenously. PET/CT was performed after 60 min of rest. The scan range is from head to the upper part of the femur. All CT images were transferred via the network to the Philips Pinnacle 9.10 treatment planning system (TPS) (Philips Healthy, Fitchburg, WI, USA), as were PET/CT images.

Table 1
Patient characteristics.

	Number of cases
Gender	
Male	23
Female	0
Age (y)	
Median	61
Range	38–81
Histology	
Squamous cell carcinoma	18
Adenocarcinoma	5
TNM stage	
IIIA	16
IIIB	7

2.3. Target and OARs delineation

Target and OARs were delineated by experienced physicians. Two delineation methods based on PET/CT and CT were adopted respectively. Based on PET/CT, the maximum standard uptake value (SUV) of FDG at the lesion was 100%, and the 50% level was set as the boundary of the gross tumor volume (GTV_{PET}) [20]. The planning gross tumor volume ($PGTV_{PET}$) was generated by uniformly expanding the GTV_{PET} by 8 mm in each direction. Clinical target volume (CTV_{PET}) was generated by uniformly extending the GTV_{PET} by 6 mm in each direction including high-risk lymph modes. The planning clinical target volume ($PCTV_{PET}$) was generated by uniformly expanding the CTV_{PET} by 8 mm in each direction.

Based on CT, the target located in lung was delineated on the lung window, with a window width of 850 HU and a window level of −750 HU. The target located at mediastinum and positive lymph nodes were delineated on the mediastinum window, with a window width of 400 HU and a window level of 20 HU. Any visible primary lesion, including all lymph nodes with a short axis diameter > 1 cm, was defined as gross tumor volume (GTV_{CT}). Planning gross target volume ($PGTV_{CT}$), clinical target volume (CTV_{CT}), and planning clinical target volume ($PCTV_{CT}$) were expanded in the same way as $PGTV_{PET}$, CTV_{PET}, and $PCTV_{PET}$, respectively.

OARs included total lung, spinal cord and heart. Total lung volume was defined as right plus left lungs minus the GTV_{PET}/GTV_{CT}。 The spinal cord was expanded by 5 mm to create planning risk volume (PRV), which was called PRV_{cord}.

2.4. Target comparison

The following parameters of GTV_{PET} and GTV_{CT} were analyzed for each image set, such as the volume, the length in each of the 3 orthogonal directions and the center of mass (COM) coordinates. In this study, X, Y, and Z represent the coordinates of the medial–lateral (ML), superior-inferior (SI), and anterior-posterior (AP) directions, respectively. In analyzing the COM differences between GTV_{PET} and GTV_{CT}, we also evaluated the absolute COM deviation, which was defined as:

$$\Delta L = \sqrt{\Delta X_{COM}^2 + \Delta Y_{COM}^2 + \Delta Z_{COM}^2}$$

where ΔX_{COM}, ΔY_{COM}, and ΔZ_{COM} were the COM coordinate differences between two volumes in ML, SI, and AP directions, respectively.

The overlapping ratio was used to evaluate overlap of GTV_{PET} and GTV_{CT}, which was defined as:

$$OR = \frac{V_{GTVPET} \cap V_{GTVCT}}{V_{GTVPET}}$$

where V_{GTVPET} and V_{GTVCT} were the volumes of GTV_{PET} and GTV_{CT}, respectively.

2.5. Treatment planning

All simultaneously integrated boost intensity-modulated radiotherapy (SIB-IMRT) treatment plannings were created in Pinnacle 9.10 planning system. All plans were generated using 4–5 coplanar beam for Edge linear accelerator (Varian, Palo Alto, CA) with 6 MV photon beam. The optimization algorithm used direct machine parameter

optimization (DMPO) and the dose calculation used collapsed cone convolution (CCC) algorithm. In all plans, dose rate was 600 MU/min, the grid resolution of dose calculation was 3 mm, and the tissue heterogeneity was corrected. Two plans were created for each patient based on two targets: Plan_PET and Plan_CT. A total of 60.2 Gy in 28 fractions was prescribed to $PGTV_{PET}$ and $PGTV_{CT}$ of which 95% received at least 100% of the prescription, and a total of 50.4 Gy in 28 fractions was prescribed to $PCTV_{PET}$ and $PCTV_{CT}$ of which 95% received at least 100% of the prescription. The constraints of OARs were as follows, total lung V_{20} (i.e., percentage of the total lung volume receiving ≥ 20 Gy) < 25%, according to the patient's physical condition increased appropriately, the maximum is not more than 30%, MLD ≤ 15 Gy, the maximum dose of spinal cord (Dmax) ≤ 45 Gy, heart V_{30} (i.e., percentage of the heart volume receiving ≥ 30 Gy) ≤ 40%, V_{40} (i.e., percentage of the heart volume receiving ≥ 40 Gy) ≤ 30%, MHD ≤ 26 Gy.

Plannings were generated by the auto-planning module in Pinnacle 9.10. For OARs, there were three clinical goals, which were Max Dose, Mean Dose and Max DVH. Each clinical goal has four priorities, which were Low, Medium, High and Constrain. The details of AP optimization settings were in Table 2.

2.6. Treatment planning evaluation

In this paper, the dosimetric differences between the two target delineation methods were compared, and dose-volume histograms (DVHs) were used to evaluate doses in the target, total lung, spinal cord and heart. The target was evaluated by D_{mean}, D_2, D_{98}, V_{95}, V_{105}, conformity index (CI) and heterogeneity index (HI). CI [10] was defined as $CI = V_{T,ref}/V_T \times V_{T,ref}/V_{ref}$, where $V_{T,\ ref}$ was the volume of PTV covered by prescription dose, V_T was the volume of the PTV, and V_{ref} was the volume covered by prescription dose. HI [21] was defined as $HI = (D_2\text{-}D_{98})/D_p$, where D_2 and D_{98} correspond to radiation doses delivered to 2% and 98% of the PTV, respectively. D_p was the prescription dose. The lower the HI value means the better radiation distribution. The evaluation parameters of OARs included MLD, V_5, V_{10}, V_{13}, V_{20}, V_{30} and V_{40} of total lung, D_{max} of the spinal cord, MHD, V_{30} and V_{40} of heart. In addition, MUs were also evaluated.

2.7. Radiobiological modeling

To evaluate the clinical effect of dose differences between treatment plans, TCP of the target and NTCP of total lung and heart were calculated. TCP calculation was based on the EUD model [22] and Matlab R2016a (The MathWorks Inc., MA, USA), and the equations were as follows:

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}}$$

$$EUD = \left[\sum_{i=1} (v_i D_i^{\alpha})\right]^{\frac{1}{\alpha}}$$

where TCD_{50} (i.e., the tumor dose to control 50% of the tumor when the tumor is homogeneously irradiated), γ_{50} (i.e., the change in TCP expected because of a 1% change in dose about the TCD_{50}) and α were 51.24 Gy, 0.83 and 0.30, respectively. D_i was a uniform dose of partial volume V_i [23].

NTCP calculation was based on Lyman-Kutcher-Burman (LKB) model [24] and Matlab program. The equations were as follows:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}dx}$$

$$t = \frac{D_{eff} - TD_{50}}{mTD_{50}}$$

$$D_{eff} = \left(\sum_i v_i D_i^{1/n}\right)^n$$

where for pneumonia, TD_{50}, n and m published by Semenko [25] were 29.9 Gy, 1 and 0.41, respectively. For pericarditis, the parameters published by Martel [26] were adopted, $TD50$ = 50.6 Gy, n = 0.64, m = 0.13.

2.8. Statistical analysis

SPSS 20.0 (IBM Corporation, Armonk, NY) statistical software was used for data analysis. A paired-samples *t*-test was used to analyze the dosimetric and biological parameters between groups, and a p-value < 0.05 was considered statistically.

3. Results

3.1. Comparison between GTV_{PET} and GTV_{CT}

The volume of GTV_{PET} and GTV_{CT} in 23 patients was 82.91 ± 58.89 cc and 135.15 ± 84.45 cc, respectively, and GTV_{PET} was significantly smaller than GTV_{CT} (p < 0.001). OR was 57.74 ± 15.65. The dimension differences between GTV_{PET} and GTV_{CT} were calculated. Compared with GTV_{PET}, the average GTV_{CT} dimension in the 3D CT images were larger by 1.49 ± 1.36 cm, 1.33 ± 1.34 cm and 1.60 ± 1.50 cm in the ML (ΔX), SI (ΔY) and AP (ΔZ) directions, respectively. We also compared the difference in COM coordinates between GTV_{PET} and GTV_{CT}. The mean shifts in COM coordinates for GTV_{CT} were −0.09 ± 0.90 cm, 0.34 ± 0.68 cm and −0.23 ± 0.80 cm in the ML (ΔX_{COM}), SI (ΔY_{COM}) and AP (ΔZ_{COM}) directions, respectively, relative to GTV_{PET}, details were shown in Table 3. Fig. 1 showed distributions of COM coordinate difference between GTV_{PET} and GTV_{CT} in the ML, SI and AP directions, respectively, and in absolute COM shift. The maximum absolute COM shift (ΔL) was 3.76 cm. In all patients analyzed, 73.9% showed ΔL > 0.5 cm.

3.2. Dose to target coverage

In this study, a total of 46 plans were created for 23 patients, all of which were considered clinically acceptable by radiation oncologist. Figs. 2 and 3 were comparisons of dose distribution and DVHs between

Table 2
Auto-planning setup template.

OARs	Objective	Dose level	Priority	Compromise
Spinal Cord	Max Dose	44 Gy	High	No
PRV_{cord}	Max Dose	45 Gy	High	No
Total Lung	Max DVH	5 Gy 30%	Medium	Yes
Total Lung	Max DVH	20 Gy 18%	Medium	Yes
Total Lung	Max DVH	30 Gy 8%	Medium	Yes
Heart	Max DVH	30 Gy 40%	Medium	Yes
Heart	Max DVH	40 Gy 30%	Medium	Yes

Table 3
Dimension difference between GTV_{PET} and GTV_{CT}.

	GTV_{PET}	GTV_{CT}	△(cm)
ML (cm)	6.31 ± 1.55^	7.80 ± 1.64^	1.49 ± 1.36^
SI (cm)	6.21 ± 1.51^	7.54 ± 1.96^	1.33 ± 1.34^
AP (cm)	5.53 ± 1.53^	7.13 ± 1.69^	1.60 ± 1.50^
ML_{COM}	−1.04 ± 4.74^^	−1.13 ± 4.10^^	−0.09 ± 0.90^
SI_{COM}	−0.07 ± 2.16^^	0.28 ± 2.10^^	0.34 ± 0.68^
AP_{COM}	99.17 ± 6.02^^	98.94 ± 5.97^^	−0.23 ± 0.80^

△ means the difference between GTV_{CT} and GTV_{PET}, ^ means length value, ^^means coordinate value.

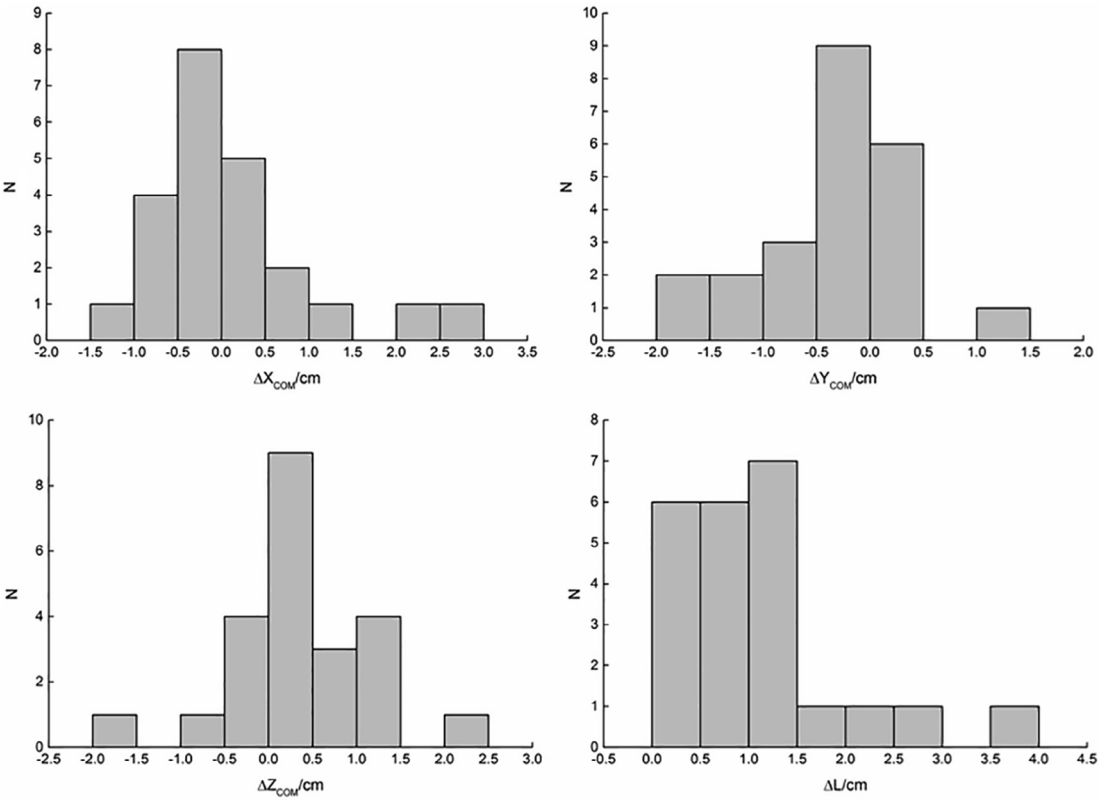

Fig. 1. Distributions of center-of-mass (COM) coordinate difference between GTV_{PET} and GTV_{CT} in the ML (ΔX_{COM}), SI (ΔY_{COM}), and AP (ΔZ_{COM}) directions, respectively, and in absolute COM shift (ΔL) for all the treatment fractions.

two plans for a patient.

D_{98} of $PGTV_{PET}$ in Plan_PET was 59.53 ± 0.11 Gy, which was slightly higher than 59.43 ± 0.18 Gy of $PGTV_{CT}$ in Plan_CT, and there was a statistical difference ($p < 0.05$). V_{95} of $PGTV_{PET}$ in Plan_PET was 99.95 ± 0.05, which was also significantly higher than 99.84 ± 0.17 of $PGTV_{CT}$ in Plan_CT ($p < 0.05$). CI of $PGTV_{PET}$ in Plan_PET was 0.84 ± 0.04, which was better than 0.82 ± 0.04 of $PGTV_{CT}$ in Plan_CT, and there was a statistical difference ($p < 0.05$). There was no significant difference in other parameters ($p > 0.05$). D_{mean}, D_2, D_{98}, V_{95}, V_{105}, CI and HI of $PGTV_{PET}$ in Plan_PET were better than those of $PGTV_{CT}$ in Plan_PET ($p < 0.05$). D_{98}, V_{95} and CI of $PGTV_{CT}$ in Plan_CT were better than those of $PGTV_{PET}$ in Plan_CT ($p < 0.05$), and there was no significant difference in other parameters ($p > 0.05$). The details were shown in Table 4.

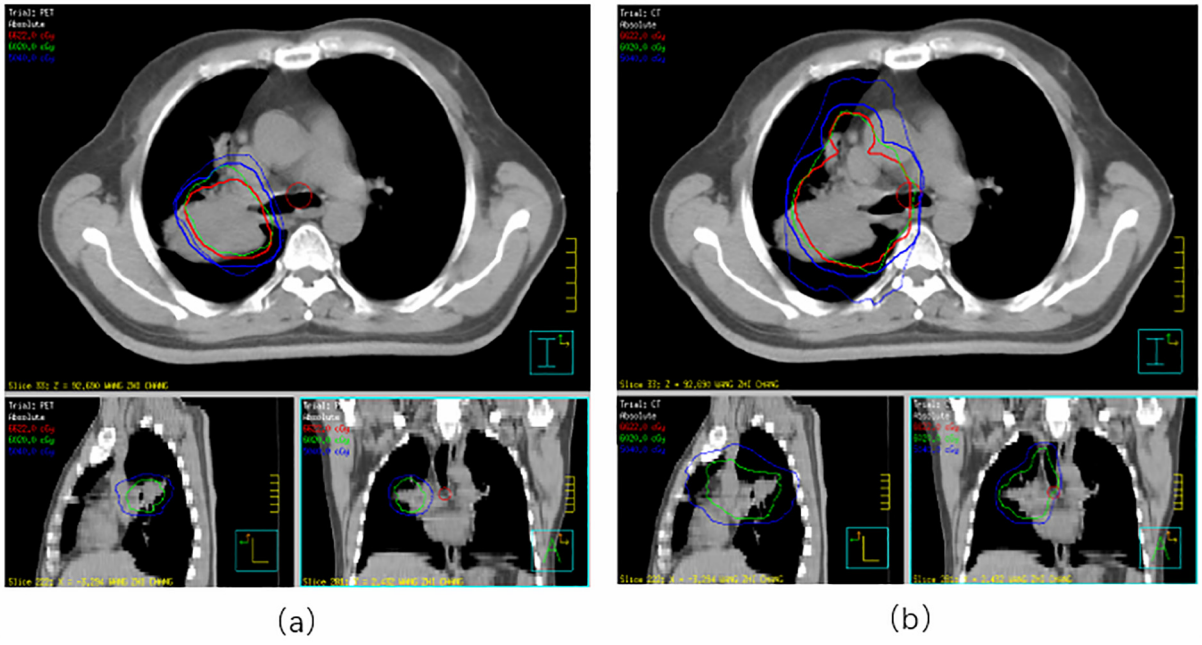

Fig. 2. The comparison of dose distribution in Plan_PET (a) and Plan_CT (b) for a patient.

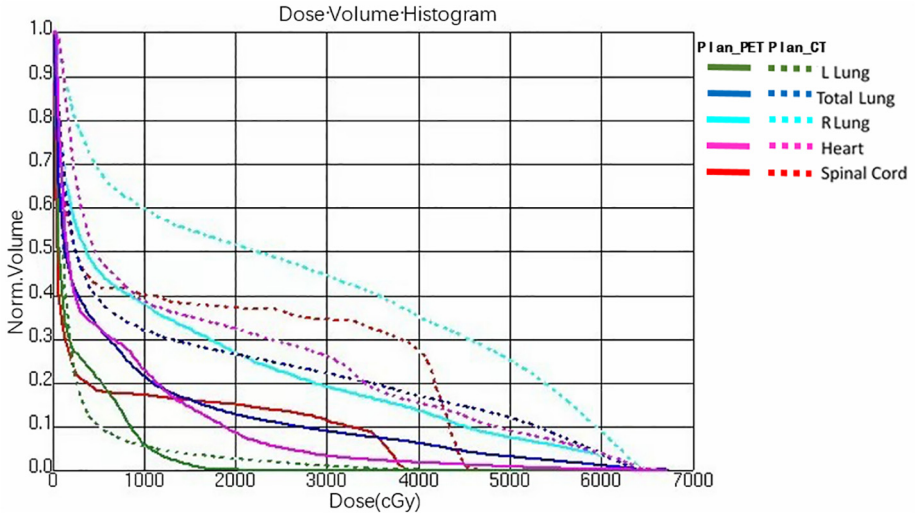

Fig. 3. The comparison of DVHs for OARs in Plan_PET and Plan_CT for a patient.

CI of $PCTV_{PET}$ in Plan_PET was better than the that of $PCTV_{CT}$ in Plan_CT ($p < 0.05$). There was no significant difference in other parameters ($p > 0.05$). D_{mean}, D_2, D_{98}, V_{95}, V_{105}, CI and HI of $PCTV_{PET}$ in Plan_PET were better than those of $PCTV_{CT}$ in Plan_PET ($p < 0.05$). The D_2 and CI of $PCTV_{CT}$ in Plan_CT were better than those of $PCTV_{PET}$ in Plan_CT ($p < 0.05$). There were no significant differences in other parameters ($p > 0.05$). The details were shown in Table 5.

3.3. Dose to total lung

The dose comparisons of total lung were shown in Table 6. MLD, V_5, V_{10}, V_{13}, V_{15}, V_{20}, V_{30} and V_{40} in Plan_PET were significantly lower than those in Plan_CT. Fig. 4. showed the specific differences in each dosimetric parameter.

3.4. Dose to spinal cord, heart and MUs

The dosimetric comparisons of spinal cord and heart were shown in Table 7. The D_{max} of spinal cord in Plan_PET was 39.29 ± 9.74 Gy, which was lower than that of Plan_CT (43.48 ± 2.32 Gy), but there was no statistical difference. For heart, MHD, V_{30} and V_{40} in Plan_PET were significantly lower than those in Plan_CT. For MUs, compared with Plan_CT (497.61 ± 95.35), MUs of Plan_PET (449.04 ± 84.41) decreased by 9.7%, and there was a statistical significance ($p < 0.05$).

3.5. TCP and NTCP

Table 8 showed TCP of target and NTCP of total lung and heart. TCP of GTV_{PET} in Plan_PET was significantly higher than that of GTV_{CT} in Plan_PET ($p < 0.05$). TCP of GTV_{CT} in Plan_CT was similar to that of GTV_{PET} in Plan_CT. NTCP of total lung in Plan_PET was significantly lower than that in Plan_CT ($p < 0.001$). The NTCP of heart in Plan_PET was also lower than that in Plan_CT, but there was no statistical significant.

4. Discussion

For LA-NSCLC patients who are not suitable for surgical resection, radiotherapy combined with chemotherapy has become the standard of treatment [27,28]. Accurate target delineation plays an important role in radiotherapy. Generally, target delineation is based on CT images, but with the development of technology, PET / CT images are applied to target delineation recently. Studies had shown that [29,30], the application of PET/CT could improve the accuracy of target delineation in 25%-50% of patients and reduce the target volume. Dosimetric differences between PET- and CT-based targets had been reported in some literatures [18,31,32]. However, in these studies, MP was used for treatment planning generation, and the staging of tumors was inconsistent, and no biological evaluation was performed. This study used AP to evaluate the dosimetric and biological differences between patients with stage IIIA-IIIB NSCLC using PET- and CT-based delineations.

AP is the development trend of TPS, and some studies [33,34] had reported the application of AP. Compared with MP, AP can better protect OARs, reduce the time of generating plans. Most importantly, AP can improve the quality of the plans and reduce the differences between one single person or different persons. Nawa et al. [13]

Table 4
Target coverage comparison for $PGTV_{PET}$ and $PGTV_{CT}$.

	Plan_PET		Plan_CT	
	$PGTV_{PET}$	$PGTV_{CT}$	$PGTV_{CT}$	$PGTV_{PET}$
D_{mean}(Gy)	63.06 ± 0.27^{+}	57.91 ± 4.92^{+}	63.10 ± 0.35	63.33 ± 0.66
D_2(Gy)	65.71 ± 0.50^{+}	65.53 ± 0.48^{+}	65.92 ± 0.69^{-}	66.01 ± 0.67^{-}
D_{98}(Gy)	59.53 ± 0.11$^{+,*}$	30.25 ± 21.51^{+}	59.43 ± 0.18*	58.05 ± 9.10
V_{95}(%)	99.95 ± 0.05$^{+,*}$	79.24 ± 14.31^{+}	99.84 ± 0.17*	99.42 ± 1.95
V_{105}(%)	49.77 ± 7.51^{+}	32.46 ± 8.97^{+}	48.37 ± 10.24^{-}	57.74 ± 10.67^{-}
CI	0.84 ± 0.04$^{+,*}$	0.61 ± 0.13^{+}	0.82 ± 0.04$^{-,*}$	0.56 ± 0.13^{-}
HI	0.10 ± 0.01^{+}	0.59 ± 0.36^{+}	0.11 ± 0.01	0.13 ± 0.15

$^{+}$ $PGTV_{PET}$ in Plan_PET vs $PGTV_{CT}$ in Plan_PET has significant difference.
$^{-}$ $PGTV_{CT}$ in Plan_CT vs $PGTV_{PET}$ in Plan_CT has significant difference.
* $PGTV_{PET}$ in Plan_PET vs $PGTV_{CT}$ in Plan_CT has significant difference.

Table 5
Target coverage comparison for $PCTV_{PET}$ and $PCTV_{CT}$.

	Plan_PET		Plan_CT	
	$PCTV_{PET}$	$PCTV_{CT}$	$PCTV_{CT}$	$PCTV_{PET}$
D_{mean}(Gy)	60.92 ± 0.66^{+}	53.97 ± 5.90^{+}	59.07 ± 10.33	61.90 ± 0.94
D_2(Gy)	65.49 ± 0.49^{+}	65.33 ± 0.49^{+}	65.72 ± 0.67^{-}	65.83 ± 0.66^{-}
D_{98}(Gy)	53.76 ± 1.52^{+}	21.15 ± 16.81^{+}	53.76 ± 0.93	53.19 ± 9.69
V_{95}(%)	99.91 ± 0.15^{+}	81.74 ± 13.85^{+}	99.87 ± 0.18	99.47 ± 2.03
V_{105}(%)	98.74 ± 1.20^{+}	74.40 ± 14.30^{+}	98.72 ± 0.80	98.93 ± 2.31
CI	0.70 ± 0.06$^{+,*}$	0.59 ± 0.14^{+}	0.66 ± 0.08$^{-,*}$	0.46 ± 0.11^{-}
HI	0.23 ± 0.03^{+}	0.88 ± 0.33^{+}	0.24 ± 0.03	0.25 ± 0.20

$^{+}$ $PCTV_{PET}$ in Plan_PET vs $PCTV_{CT}$ in Plan_PET has significant difference.
$^{-}$ $PCTV_{CT}$ in Plan_CT vs $PCTV_{PET}$ in Plan_CT has significant difference.
* $PCTV_{PET}$ in Plan_PET vs $PCTV_{CT}$ in Plan_CT has significant difference.

Table 6
Dosimetric parameters between Plan_PET and Plan_CT.

	Plan_PET	Plan_CT	P value
MLD(Gy)	8.04 ± 3.30	10.49 ± 3.69	< 0.001*
V_5(%)	26.85 ± 11.21	34.46 ± 11.08	< 0.001*
V_{10}(%)	20.47 ± 9.32	27.88 ± 12.80	< 0.001*
V_{13}(%)	18.26 ± 8.67	23.55 ± 9.63	< 0.001*
V_{15}(%)	17.10 ± 8.27	21.93 ± 9.14	< 0.001*
V_{20}(%)	14.60 ± 7.28	18.80 ± 8.11	< 0.001*
V_{30}(%)	10.59 ± 5.54	14.23 ± 6.70	< 0.001*
V_{40}(%)	7.18 ± 4.13	10.07 ± 5.21	< 0.001*

* Significant difference.

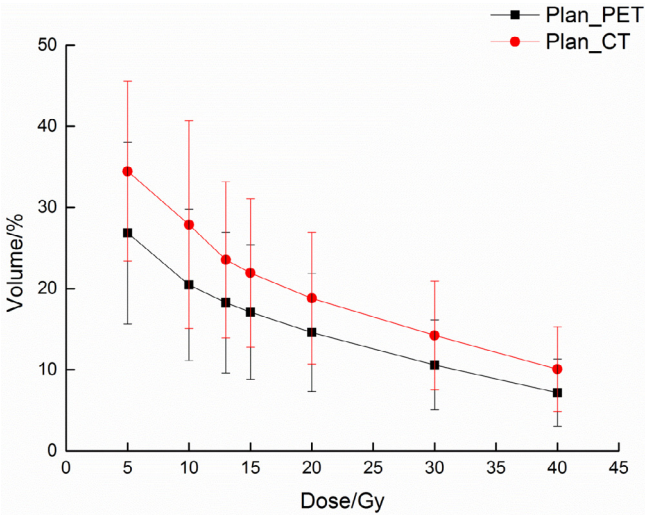

Fig. 4. The difference of V_5, V_{10}, V_{13}, V_{15}, V_{20}, V_{30}, V_{40} between Plan_PET and Plan_CT.

Table 7
Comparison of spinal cord, heart and MUs.

	Plan_PET	Plan_CT	P value
Spinal Cord			
D_{max} (Gy)	39.29 ± 9.74	43.48 ± 2.32	0.063
Heart			
MHD (Gy)	11.26 ± 6.72	15.02 ± 7.94	0.004*
V_{30} (%)	15.11 ± 10.77	23.92 ± 12.16	< 0.001*
V_{40} (%)	8.45 ± 7.39	15.67 ± 9.69	< 0.001*
MU	449.04 ± 84.41	497.61 ± 95.35	0.008*

* Significant difference.

reported that for prostate cancer, AP was better than MP, and significantly reduced the differences between planners. Therefore, in this study, dosimetric and biological comparisons were performed in patients with LA-NSCLC who were unsuitable for surgical resection using AP. It can guarantee the consistency of plans and it can also remove inter and intra planner variability.

Tumor staging is one of the most important factors in the rational choice of treatment and prognosis of NSCLC. In many existing studies, the patient staging span was large, which led to a decrease in the consistency of the results. In this study, 23 patients with stage IIIA-IIIB NSCLC were selected. The patients were relatively concentrated in stages, and the results were more accurate.

The volume and dimension differences of GTV_{PET} and GTV_{CT} were compared in this study. Compared with GTV_{CT}, the volume of GTV_{PET} decreased significantly ($p < 0.001$), and the target length was smaller in ML, SI and AP directions. The results were similar to those of Leclerc [35] and Daisne [36]. In COM coordinate system, the COM of GTV_{PET} and GTV_{CT} had great differences in ML, SI and AP directions. In 73.9% of cases, the absolute COM deviation is more than 0.5 cm.

The target dosimetric results of $PGTV_{PET}$ and $PGTV_{CT}$ in Plan_PET (see Table 4) showed that Dmean, D_2, D_{98}, V_{95}, V_{105}, CI and HI of $PGTV_{CT}$ were worse than those of $PGTV_{PET}$ ($p < 0.05$), which could not meet the clinical requirements. This might be that the volume of GTV_{PET} was significantly smaller than the volume of GTV_{CT}. Therefore, careful consideration should be given when only using PET/CT to delineate the target.

The target dosimetric results of $PGTV_{CT}$ and $PGTV_{PET}$ in Plan_CT (see Table 4) showed that D_2 and V_{105} of $PGTV_{PET}$ were significantly higher than those of $PGTV_{CT}$ because $PGTV_{PET}$ was smaller than $PGTV_{CT}$ and was located at a higher dose region. CI of $PGTV_{PET}$ in Plan_CT was worse than that of $PGTV_{CT}$ because the volume of GTV_{PET} was significantly smaller than that of GTV_{CT}. The volume covered by the prescription isodose in Plan_CT was much larger than that of $PGTV_{PET}$, so CI was worse.

In this study, the volume of $PGTV_{PET}$ in 4 out of 23 patients exceeded that of $PGTV_{CT}$. The reason was that the COM of GTV_{PET} and GTV_{CT} were quite different. Even if the volume of GTV_{CT} was much larger than that of GTV_{PET}, GTV_{PET} could not be completely covered by GTV_{CT}. Therefore, careful consideration should also be given when only using CT to delineate the target. The best way to delineate the target is to delineate the target in the fusion images of PET/CT and CT.

Radiation pneumonitis (RP) is one of the most common complications in radiotherapy of thoracic tumors. Studies had shown the relationship between RP and dosimetric factors [37]. Dosimetric factors such as MLD and percentage of lung volume receiving over-threshold radiation dose showed predictability of RP [38,39]. Schallenkamp et al. [40] reported that V_{20} and MLD were important predictors of RP. Wang et al. [41] reported that several DVH parameters (V_5 to V_{65} and MLD of total lung) were highly correlated with RP. Therefore, the radiation dose to total lung should be reduced as much as possible, especially to

Table 8
TCP and NTCP.

TCP (%)				NTCP (‰)			
Plan_PET		Plan_CT		Plan_PET		Plan_CT	
GTV_{PET}	GTV_{CT}	GTV_{PET}	GTV_{CT}	Lung	Heart	Lung	Heart
67.66 ± 0.42[-]	63.97 ± 5.45[-]	67.69 ± 0.56	67.57 ± 0.44	41.64 ± 21.48*	0.04 ± 0.16	64.94 ± 31.20*	0.27 ± 0.64

[-] GTV_{PET} in Plan_PET vs GTV_{CT} in Plan_PET has significant difference.
* Lung in Plan_PET vs Lung in Plan_PET has significant difference.

reduce the low dose volume of the total lung. Compared with Plan_CT, Plan_PET significantly improved the V_5, V_{10}, V_{13}, V_{15}, V_{20}, V_{30}, V_{40} and MLD of total lung, which could better protect total lung. This was due to the fact that the volume of GTV_{PET} was significantly smaller than that of GTV_{CT}.

The study of MUs showed that the MUs of Plan_PET was 9.76% lower than that of Plan_CT, and there was significant difference. Though the absolute difference was small, it showed that the treatment efficiency of Plan_PET was slightly higher than that of Plan_CT.

The biological evaluation of PET- and CT-based delineation methods in Table 8 showed that in Plan_PET, TCP of GTV_{PET} was superior to TCP of GTV_{CT}. In Plan_CT, TCP of GTV_{CT} was equivalent to TCP of GTV_{PET}. In the 4 patients whose GTV_{PET} volume exceeded the GTV_{CT} volume mentioned above, TCP of GTV_{PET} was slightly lower than that of GTV_{CT}. The biological indicators proved that those 4 patients needed to delineate target based on fusion images of PET/CT and CT.

For NTCP of total lung, Plan_PET was significantly lower than Plan_CT, because the volume of GTV_{PET} is smaller than the volume of GTV_{CT}. For NTCP of heart, Plan_CT was about 7 times that of Plan_PET, but the absolute values of both NTCP were very small. The reason may be that heart was far from the tumor and received less doses. Similar results had been obtained in studies published by Münch [42], in which the dose distribution of heart was strongly dependent on the location of the tumor.

The limitation of this work was that the sample size was small and it was a retrospective study, which might have selective bias. Prospective, large sample size research might be done to make the results more accurate. In this study, 50% SUV_{max} was selected as the boundary of the PET-based target. Delineating the target with different thresholds may result in different results. Compared to simple threshold-based approaches, approaches based on more advanced image segmentation and analysis paradigms will be higher accuracy and robustness [43]. Finally, further studies are needed for patients with atelectasis and pneumonectomy.

5. Conclusions

In this study, the dosimetric and biological differences of LA-NSCLC PET- and CT-based delineation methods were studied using AP. AP can reduce individual differences and improve the quality of treatment plans. The volume, boundary and COM of the target based on the two delineation methods were different and could not be included in each other, and led to the differences of dosimetric and biological indicators. Therefore, the way that most hospitals only use CT images to delineate the target for LA-NSCLC needs careful consideration.

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References

[1] Ren CB, Ji TL, Liu TL, Dang J, Li G. The risk and predictors for severe radiation pneumonitis in lung cancer patients treated with thoracic reirradiation. Radiat Oncol 2018;13(1):69.
[2] Machtay M, Bae K, Movsas B, Paulus R, Gore E, Komaki R, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non–small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 2012;82(1):425–34.
[3] Curran WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9401. J Natl Cancer Inst 2011;103(19):1452–60.
[4] Beyer T, Townsend DW, Brun T, Kinahan PE, Charron M, Roddy R, et al. A combined PET/CT scanner for clinical oncology. J Nucl Med 2000;41:1369–79.
[5] Czernin J, Allen-Auerbach M, Schelbert HR. Improvements in cancer staging with PET/CT : literature-based evidence ai of September 2006. J Nucl Med 2007;48(Suppl. 1):78S–88S.
[6] Nestle U, Weber W, Hentschel M, Grosu AL. Biological imaging in radiation therapy: role of positron emission tomography. Phys Med Biol 2009;54:R1e25.
[7] Mohammad Hussein, South CP, Barry MA. Clinical validation and benchmarking of knowledge-based IMRT and VMAT treatment planning in pelvic anatomy. Radiother Oncol 2016. S0167814016311823.
[8] Wu B, Kusters M, Kunzebusch M, Dijkema T, McNutt T, Sanguineti G, et al. Cross-institutional knowledge-based planning (KBP) implementation and its performance comparison to Auto-Planning Engine (APE). Radiother Oncol 2017;123(1):57.
[9] Wang S, Zheng D, Zhang C, Ma R, Bennion NR, Lei Y, et al. Automatic planning on hippocampal avoidance whole-brain radiotherapy. Med Dosim 2017;42(1):63–8.
[10] Fan J, Wang J, Zhang Z, Hu WG. Iterative dataset optimization in automated planning: implementation for breast and rectal cancer radiotherapy. Med Phys 2017;44(6):2515–31.
[11] Evaluation of an automated knowledge based treatment planning system for head and neck.
[12] Nawa K, Haga A, Nomoto A, Sarmiento RA, Shiraishi K, Yamashita H, et al. Evaluation of a commercial automatic treatment planning system for prostate cancers. Med Dosim 2017;42(3):203–9.
[13] Hatt M, Rest CC, Baardwijk AV, Lambin P, Pradier O, Visvikis D. Impact of tumor size and tracer uptake heterogeneity in (18) F-FDG PET and CT non-small cell lung cancer tumor delineation. J Nucl Med 2011;52(11):1690.
[14] Yu HM, Liu YF, Hou M, Liu J, Li XN, Yu JM. Evaluation of gross tumor size using CT, 18F-FDG PET, integrated 18F-FDG PET/CT and pathological analysis in non-small cell lung cancer. Eur J Radiol 2009;72(1):104–13.
[15] Prathipati A, Manthri RG, Subramanian BV, Das P, Jilla S, Mani S, et al. A prospective study comparing functional imaging (F-FDG PET) versus anatomical imaging (Contrast Enhanced CT) in dosimetric planning for non-small cell lung cancer. Asia Oceania J Nucl Med Biol 2017;5(2):75–84.
[16] Cheebsumon P, Boellaard R, De Ruysscher D, Elmpt WV, Baardwijl AV, Yaqub M, et al. Assessment of tumour size in PET/CT lung cancer studies: PET-and CT-based methods compared to pathology. EJNMMI Res 2012;2(1):56.
[17] Leclerc M, Lartigau E, Lacornerie T, Daisne JF, Kramar A, et al. Primary tumor delineation based on 18FDG PET for locally advanced head and neck cancer treated by chemo-radiotherapy. Radiother Oncol 2015;116(1):87–93.
[18] Thorwarth D, Geets X, Paiusco M. Physical radiotherapy treatment planning based on functional PET/CT data. Radiother Oncol 2010;96(3):317–24.
[19] Bradley J, Bae K, Choi N, Forster K, Siegel B, Brunetti J, et al. A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non–small-cell lung cancer (NSCLC): primary analysis of Radiation Therapy Oncology Group (RTOG) 0515. Int J Radiat Oncol Biol Phys 2012;82(1):435–441 e1.
[20] Raman S, Bissonnette JP, Warner A, Le L, Bratman S, Leighl N, et al. Rationale and protocol for a canadian multicenter phase II randomized trial assessing selective metabolically adaptive radiation dose escalation in locally advanced non–small-cell lung cancer (NCT02788461). Clin Lung Cancer 2018.
[21] Chen H, Wang H, Gu HL, Shao Y, Cai XW, Fu XL, et al. Study for reducing lung dose of upper thoracic esophageal cancer radiotherapy by auto-planning: volumetric-modulated arc therapy vs intensity-modulated radiation therapy. Med Dosim 2018;43(3):243–50.
[22] Gay HA, Niemierko A. A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy. Physica Med 2007;23(3–4):115–25.
[23] Huang BT, Lu JY, Lin PX, Chen JZ, Li DR, Chen CZ. Radiobiological modeling analysis of the optimal fraction scheme in patients with peripheral non-small cell lung cancer undergoing stereotactic body radiotherapy. Sci Rep 2015;5:18010.
[24] Mohan R, Mageras GS, Baldwin B, Brewster LJ, Kutcher GJ, Leibel S, et al. Clinically

relevant optimization of 3-D conformal treatments. Med Phys 1992;19:933–44.
[25] Semenenko VA, Li XA. Lyman-Kutcher-Burman NTCP model parameters for radiation pneumonitis and xerostomia based on combined analysis of published clinical data. Phys Med Biol 2008;53:737–55.
[26] Martel MK, Sahijdak WM, Ten Haken RK, Kessler ML, Turrisi AT. Fraction size and dose parameters related to the incidence of pericardial effusions. Int J Radiat Oncol Biol Phys 1998;40:155–61.
[27] Aupérin A, Pechoux CL, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28(13):2181–90.
[28] Curran WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III Trial RTOG 9410. J Natl Cancer I 2011;103(19):1452–60.
[29] Levine M, Julian J. Imaging: PET–CT imaging in non-small-cell lung cancer. Nat Rev Clin Oncol 2009;6(11):619.
[30] Grégoire V, Haustermans K, Geets X, Roels S, Lonneux M. PET-based treatment planning in radiotherapy: a new standard? J Nucl Med 2007;48(1):68S.
[31] Greco C, Rosenzweig K, Cascini GL, Tamburrini. Current status of PET/CT for tumour volume definition in radiotherapy treatment planning for non-small cell lung cancer (NSCLC). Lung cancer 2007;57(2):125–34.
[32] Leclerc M, Lartigau E, Lacornerie T, Daisne JF, Kramar A, Gregoire. Primary tumor delineation based on 18FDG PET for locally advanced head and neck cancer treated by chemo-radiotherapy. Radiother Oncol 2015;116(1):87–93.
[33] Hazell I, Bzdusek K, Kumar P, Hansen CR, Bertelsen A, Eriksen JG, et al. Automatic planning of head and neck treatment plans. J Appl Clin Med Phys 2016;17(1):272–82.
[34] Li X, Wang L, Wang JH, Han X, Xia B, Wu SX, et al. Dosimetric benefits of automation in the treatment of lower thoracic esophageal cancer: is manual planning still an alternative option? Med Dosim 2017;42(4):289–95.
[35] Leclerc M, Lartigau E, Lacornerie T, Daisne JF, Kramar A, Gregoire V. Primary tumor delineation based on 18FDG PET for locally advanced head and neck cancer treated by chemo-radiotherapy. Radiother Oncol 2015;116(1):87–93.
[36] Daisne JF, Duprez T, Weynand B, Lonneux M, Hamolr M, Reychler H, et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen 1. Radiology 2004;233(1):93.
[37] Boonyawan K, Gomez DR, Komaki R, Xu YJ, Nantavithya C, Allen PK, et al. Clinical and Dosimetric Factors Predicting Grade ≥2 Radiation Pneumonitis after Postoperative Radiotherapy for Patients with Non-Small Cell Lung Carcinoma. Int J Radiat Oncol Biol Phys 2018;S0360301618306631.
[38] Bentel GC. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 2001;51(3):650–9.
[39] Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, et al. Clinical dose–volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45(2):323–9.
[40] Schallenkamp JM, Miller RC, Brinkmann DH, Foote T, Garces YI. Incidence of radiation pneumonitis after thoracic irradiation: dose-volume correlates. Int J Radiat Oncol Biol Phys 2007;67(2):410–6.
[41] Wang S, Liao ZX, Wei X, Liu HH, Tucker SL, Hu CS, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). Int J Radiat Oncol Biol Phys 2006;66(5):1399–407.
[42] Münch S, Oechsner M, Combs SE, et al. DVH- and NTCP-based dosimetric comparison of different longitudinal margins for VMAT-IMRT of esophageal cancer. Radiat Oncol 2017;12(1):128.
[43] Hatt M, Lee J, Schmidtlein CR, Naqa IE, Caldwell C, Bernardi ED, et al. Classification and evaluation strategies of auto-segmentation approaches for PET: report of AAPM task group No. 211. Med Phys 2017;44(6):e1–42.