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Voxel-Level BED Corrected Dosimetric and Radiobiological Assessment of 2 Kinds of Hybrid Radiotherapy Planning Methods for Stage III NSCLC

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Abstract

Background/purpose: To access the comparative dosimetric and radiobiological advantages of two methods of intensity-modulated radiation therapy (IMRT)-based hybrid radiotherapy planning for stage III nonsmall cell lung cancer (NSCLC). **Methods:** Two hybrid planning methods were respectively characterized by conventional fraction radiotherapy (CFRT) and stereotactic body radiotherapy (SBRT) and CFRT and simultaneous integrated boost (SIB) planning. All plans were retrospectively completed using the 2 methods for 20 patients with stage III NSCLC. CFRT and SBRT dose regimes 2 Gy × 30 f and 12.5 Gy × 4 f were, respectively, used for planning target volume of lymph node (PTV_{LN}) and planning target volume of the primary tumor (PTV_{PT}), while dose regimes 2 Gy × 26 f for PTV_{LN} and sequential 2 Gy × 4 f for PTV_{LN} combined with 12.5 Gy × 4 f for PTV_{PT} were adopted for CFRT and SIB plans. SBRT and SIB EQD_2 dose were calculated voxel by voxel, and then, respectively, superimposed with 30-fraction and 26-fraction CFRT plan dose to achieve biological equivalent dose (BED) dosimetric parameters of CFRT and SBRT and CFRT and SIB plans. Tumor control probability (TCP)/normal tissue complication probability (NTCP) was, respectively, calculated by equivalent uniform dose/Lyman–Kutcher–Burman models. BED plan parameters and TCP/NTCP were analyzed between 2 methods of hybrid planning. Primary tumor/lymph node (LN)/total TCP values were, respectively, evaluated as a function of the radiation dose needed to control 50% of tumor (TCD_{50}) for 20 patients. Dosimetric errors were analyzed by nontransit electronic portal imaging device dosimetry measurement during hybrid plan delivery. **Results:** Statistically lower BED plan parameters of PTV_{LN} D_2 and homogeneity index resulted in slightly lower averaged LN/total TCP curves by CFRT and SIB planning. The gaps between Max and Min LN/total TCP curves were significantly closer for CFRT and SIB planning, which indicated better robustness of LN/total TCPs. A lower esophagus dose resulted in a lower esophagus NTCP by CFRT and SIB planning, which may be compromised by 1 week shorter overall treatment time by CFRT and SIB irradiation. Spinal cord D_{max} was significantly reduced by CFRT and SIB plans. The dose verification results of the subplans involved in hybrid plans were acceptable, which showed that the 2 methods of hybrid planning could be delivered accurately in our center. **Conclusion:** CFRT and SIB plannings have more advantages on BED plan parameters and TCP/NTCP than CFRT and SBRT planning, and both methods of IMRT-based hybrid planning could be executed accurately for stage III NSCLC. The effectiveness of the results needs to be validated in the hybrid trial.

Keywords

Stage III NSCLC, hybrid planning, BED plan parameters, TCP/NTCP

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Abbreviations

CT, computed tomography; AIP-CT, average intensity projection CT; BED, biological equivalent dose; CCRT, concurrent chemoradiotherapy; CFRT, conventional fraction radiotherapy; DVH, dose-volume histogram; EPID, electronic portal imaging device; EUD, equivalent uniform dose; IMRT, intensity-modulated radiation therapy; LCR, local control rate; MHD, mean heart dose; MIP-CT, maximum intensity projection CT; MLD, lung mean dose; NSCLC, nonsmall cell lung cancer; NTCP, normal tissue complication probability; OAR, organ at risk; OTT, overall treatment time; PT, primary tumor; RP, radiation pneumonitis; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiotherapy; SIB, simultaneous integrated boost; TCD_{50}, radiation dose needed to control 50% of tumor; TCP, tumor control probability; TCP_{PT}, PT TCP; VMAT, volumetric modulated arc therapy; C & S planning, CFRT and SBRT planning; C & SIB, CFRT and SIB planning

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Background

For unresectable stage III nonsmall cell lung cancer (NSCLC), primary tumor (PT) and regional lymph nodes (LNs) both had a recurrence possibility according to several evidential trials by definitive concurrent chemoradiotherapy (CCRT),[1–3] while conventional fraction radiotherapy (CFRT) was used. A reasonable and effective treatment for stage III NSCLC could be CFRT combined with stereotactic body radiotherapy (SBRT) boost. One important strategy is to use CFRT for PT and LNs followed by SBRT for residual PT and LNs disease.[4–7] This requires us to face another challenge that dose escalation to the mediastinal region (eg, esophagus and heart) in both CFRT as SBRT[8–11] may have a risk to increase the possibility of severe toxicity events, such as esophageal and cardiac radiation injury and finally a negative impact on overall survival.[8,12,13]

From the results of two studies on the pattern of locoregional failure,[14,15] it was observed that PT recurrences occurred more often than lymph node (LN) recurrences. Based on these evidential trials, we are more confident that appropriate hybrid radiotherapy should include SBRT to PT followed by image-guided adaptive CFRT to LNs (called CFRT & SBRT). The result of a recent clinical trial[16] using CFRT & SBRT planning showed that irradiation up to ≥100 Gy of biological equivalent dose (BED) (target $\alpha/\beta = 10$) achieved a 76% crude local control rate (LCR) during a 2-year follow-up survey for stage III lung cancer while the overall treatment time (OTT) ≤60 days was allowed.

For CFRT & SBRT planning, the conformality index of target dose coverage is affected by the interaction effect of the two components of hybrid planning, and it would be more significant when the distance between PT and LNs is closer. To relieve the interaction effect, an alternative option was proposed by Peulen et al[17] that simultaneous integrated boost (SIB) was used to irradiate both PT and LNs, and then LNs were treated by the rest fractions of CFRT (called CFRT & SIB).

Two possible options may be challenging for not only the uncertainty of the interaction effect from two subplans of different hybrid methods but also the differences in linac parameters settings in the optimization process.

For linac parameters settings, compared to the jaw auto-chosen method applied for intensity-modulated radiation therapy (IMRT)-based CFRT & SBRT planning, which were, respectively, optimized, the fixed jaw method was inevitably adopted in IMRT-based SIB components of CFRT & SIB planning, which was optimized in a single process. Fields jaws of SIB plans were, respectively, adaptive to PT and LNs disease, and the fixed jaw method needs to be used to reduce the delivery of PT and LNs beams to LNs and PT in a single optimization process.

The differences in the interaction effect and linac parameters settings may result in the difference in the physical and BED plan parameters, and BED is an established measure for quantifying the expected biological effect of different radiation dose fractionation schedules.[18–20] The difference may further lead to the difference in radiobiological response, including tumor control probability (TCP) and normal tissue complication probability (NTCP).[21–23] A question emerges concerning which hybrid planning technology is better with regard to tumor irradiation and organs at risk (OARs) safety.

Another concern is that TCPs of PT and LNs treated by different dose regimes differ from each other. Yeon et al[16] reported that for stage III lung cancer, all in-field recurrences/out-field regional recurrences arise in the locations of LNs disease treated by CFRT plans, not in lung fields treated by SBRT plans. The result was consistent with a basic principle implied in the TCP model[24,25] that in the context of meeting dose constraints of OARs, different types of tumors receiving different dose regimes would have different TCPs, and a higher EQD_2 dose would result in a higher TCP. TCP value was also featured by the parameter of radiation dose needed to control 50% of tumor (TCD_{50}),[22,26] and different TCD_{50} ranging from 50 to 80 Gy were observed for lung cancer patients from several previous studies.[27,28]

The main problem that we are facing to evaluate the LCR of stage III NSCLC patients treated by hybrid radiotherapy is that the individual TCP value is determined by the hybrid planning method, dose regime, and TCD_{50}. The hybrid planning method and TCD_{50}-specific TCP values with a certain dose regime would be analyzed in this work. It could fully evaluate PT/LNs/total TCP values as a function of TCD_{50} for 20 stage III NSCLC patients treated by both methods of hybrid planning. For the simulation of TCP values, the equivalent uniform dose (EUD) model has been chosen.[24,25] EUD is the homogeneous dose inside an organ that has the same clinical effect as a given, arbitrary dose distribution.[29]

Hybrid planning involves various optimization steps, which results in hybrid plans, especially SIB plans are highly modulated radiotherapy plans. Dosimetric errors between the planned and the delivered dose may result from the uncertainties in beam data measurement/modeling and/or radiation plan delivery of the highly modulated plans. The delivery accuracy of hybrid plans determines the feasibility of IMRT-based hybrid planning in the treatment of stage III NSCLC.

The comparative advantages of two methods of IMRT-based hybrid planning were evaluated in this work. BED plan parameters and TCP/NTCP were analyzed between two methods of hybrid radiotherapy planning for 20 stage III NSCLC patients. The hybrid planning method and TCD_{50}-specific PT/LNs/total TCP values were evaluated for 20 NSCLC patients. Dosimetric errors by nontransit electronic portal imaging device (EPID) measurement were checked to evaluate the feasibility of IMRT-based hybrid planning.

Materials and Methods

Patient Selection

Twenty patients with stage III NSCLC were retrospectively enrolled in this hybrid planning study from February 2015 to August 2019 (Table 1). We have obtained informed consent from the study participants or their families in a verbal version; they agreed that all treatment data of patients could be used in this study. The patients need to meet the conditions, including PT volume ≤15 cc, and the separation distance between PT and LNs disease ≥5 cm. In the 3D domain, the separation distance between PT and LNs disease was measured on a 1-slice computed tomography (CT) image when PT and LNs spatially separated on the same slice, otherwise, the separation distance was calculated by the root mean square of the spacing distance in three-dimensional direction (superior inferior, anterior posterior, left right directions).

Table 1. Patient Characteristics

Factors		
Sex	Male	18
	Female	2
Age (years)	Median (range)	62 (46-71)
Location (lobe)	Right upper	10
	Right middle	1
	Right lower	5
	Left upper	2
	Left lower	2
Clinical stage	IIIA	9
	IIIB	11
Radiotherapy sequence	CFRT before SBRT boost	3
	CFRT after SBRT boost	17
PTV_{PT} volume (cc)	Median (range)	30.7 (10.9-100.1)
PTV_{LN} volume (cc)	Median (range)	199.5 (24.8-452.3)

Abbreviations: CFRT, conventional fraction radiotherapy; SBRT, stereotactic body radiotherapy; PTV_{PT}, planning target volume of the primary tumor; PTV_{LN}, planning target volume of the lymph node.

SBRT boost to PT followed by CFRT to LNs was adopted by 17 patients, while CFRT to LNs followed by SBRT boost to PT was executed for the other 3 patients due to superior vena cava seriously compressed by enlarged LNs disease.

Treatment Preparation

Four-dimensional planning CT was acquired for each patient including the entire lung. Nine respiratory phases CT images with 3-mm thickness were, respectively, reconstructed by a Siemens CT scanner SOMATOM Definition AS (Siemens Medical Systems) and then exported to MIM Maestro 6.6.5 (MIM Software). Maximum intensity projection CT (MIP-CT) and average intensity projection CT (AIP-CT) were, respectively, reconstructed.

lymphonodus of clinical target volume (CTV_{LN}) was contoured on AIP-CT with mediastinal window-level, which was registered with diagnostic fluorodeoxyglucose positron emission tomography (PET)/CT. The planning target volume of the lymph node (PTV_{LN}) was 8 mm uniformly expanded from CTV_{LN}. Inter target volume (ITV) was contoured on MIP-CT with lung window-level, and then PTV_{PT} was 5 mm uniformly expanded from ITV. PTV margin was appropriately adjusted by the actual tumor motion. A second dedicated radiation oncologist with at least 5 years of experience checked all contours.

CFRT and SBRT Planning

All CFRT and SBRT plannings (C & S plannings) formed were retrospectively made on AIP-CT by an experienced physicist. The C & S planning method is shown in Figure 1. Dose regime 2 Gy × 30 f was used for the CFRT plan, while dose regime 12.5 Gy × 4 f was adopted for all SBRT plans for a fair comparison in this study. EDGE Linac (Varian) was used for hybrid planning in a Pinnacle 9.10 planning system.

Five to eight step-and-shoot IMRT fields using a 6 MV X-ray were adopted in all CFRT plans for PTV_{LN}, and the method has been shown in our previous work.[30] The direct machine parameter optimization algorithm was used for CFRT plans optimization and Collapsed Cone Convolution Superposition algorithm was adopted for dose calculation with a 2.5 mm dose grid. The centroid of PTV_{LN} was set as the isocenter of the IMRT fields, and appropriate delivery directions were used for CFRT fields for irradiation reduction to PTV_{PT}.

Nine to 11 coplanar single-segment IMRT fields were used for the PTV_{PT} SBRT boost plan which was different from three-dimensional conformal radiation therapy planning with 8 to 12 noncoplanar fields,[31] and the method was proposed in our another study.[32] To increase the robustness of possible interplay effects that are known from highly modulated IMRT irradiations and high-dose rates in relation to moving targets, each IMRT field with a single modulated segment was produced in an optimization process. The minimum projection size of the PTV_{PT} from all beams' eye views was set as the minimum size of segment aperture to achieve sufficient dose coverage of the moving target and a steeper dose drop gradient. The

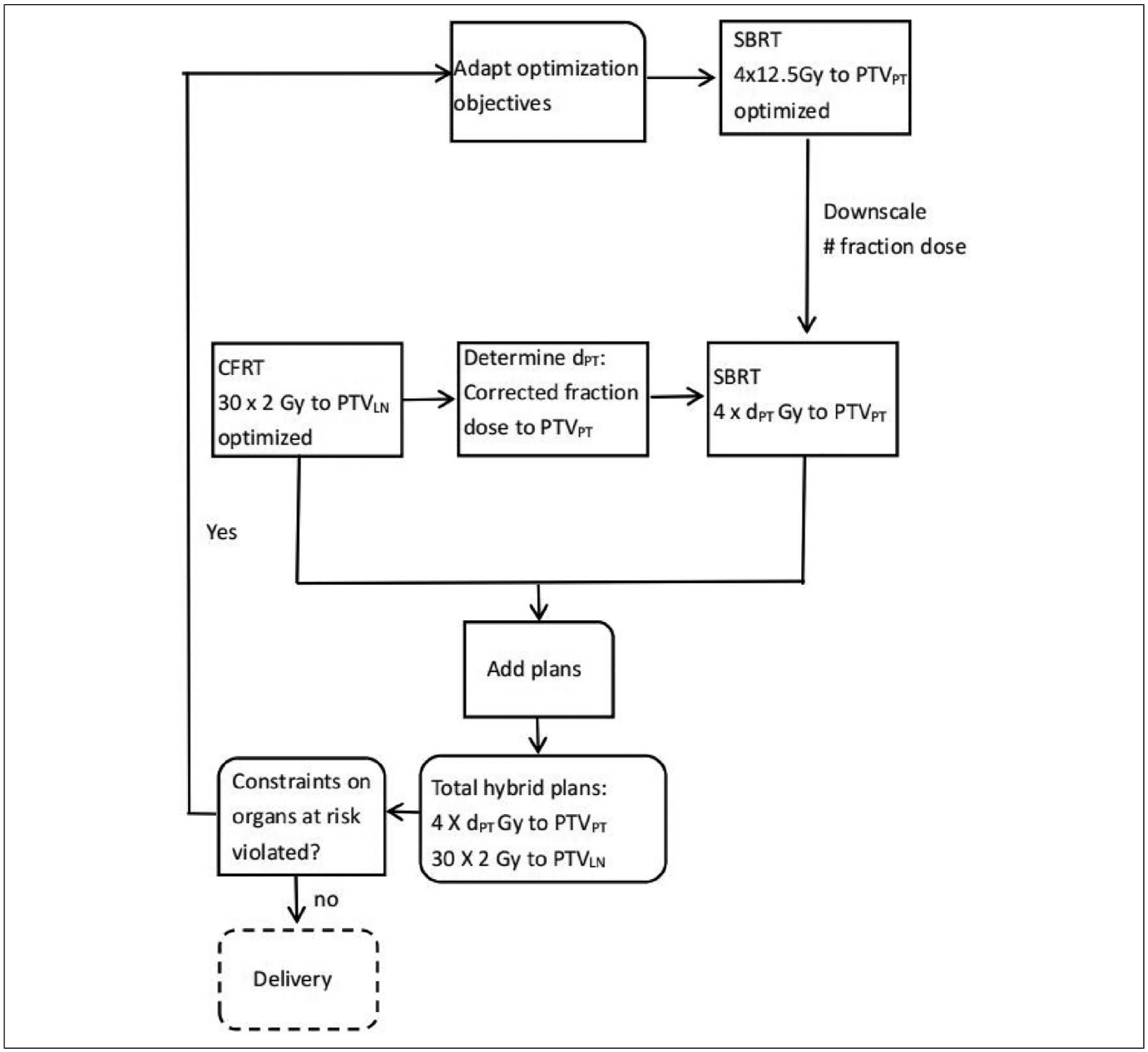

Figure 1. Flowchart of conventional fraction radiotherapy & stereotactic body radiotherapy (C & S) hybrid planning.

centroid of PTV_{PT} was set as the isocenter of SBRT fields, and appropriate delivery directions were also used for SBRT fields for irradiation reduction to PTV_{LN}. EQD_2 prescription dose actually needed for PTV_{PT} was achieved by the reduction of PTV_{PT} unintended dose (D_{99}) from the CFRT plan, and then the actual fraction dose of SBRT was downscaled by the actually needed EQD_2 dose of PTV_{PT}.

CFRT and SIB Planning

All CFRT and SIB plannings (C & SIB plannings) formed were also retrospectively made on AIP-CT by the same experienced physicist, and the flowchart of C & SIB planning is shown in Figure 2. Dose regime 2 Gy × 26 f was used for CFRT plans, while sequential dose regime 2 Gy × 4 f to LNs with 12.5 Gy × 4 f to PT was adopted for all SIB plans. Twenty-six fractions of CFRT plans were downscaled from 30 fractions CFRT plans of C & S hybrid plans. Beam numbers and directions of IMRT-based SIB plans were set as the same as the total beams used in CFRT and SBRT plans for C & S hybrid planning. SIB beams with appropriate delivery directions were, respectively, used for irradiation to PTV_{PT} and PTV_{LN}. The fixed jaw method was used for IMRT beams, respectively, for PT and LNs disease to restrict dose delivery to LNs and PT. EQD_2 prescription dose actually needed for PTV_{PT} was also achieved by the reduction of PTV_{PT} unintended dose (D_{99}) from 26 fractions CFRT plans, and then the actual fraction dose for PTV_{PT} was downscaled by actually needed EQD_2 dose of PTV_{PT}.

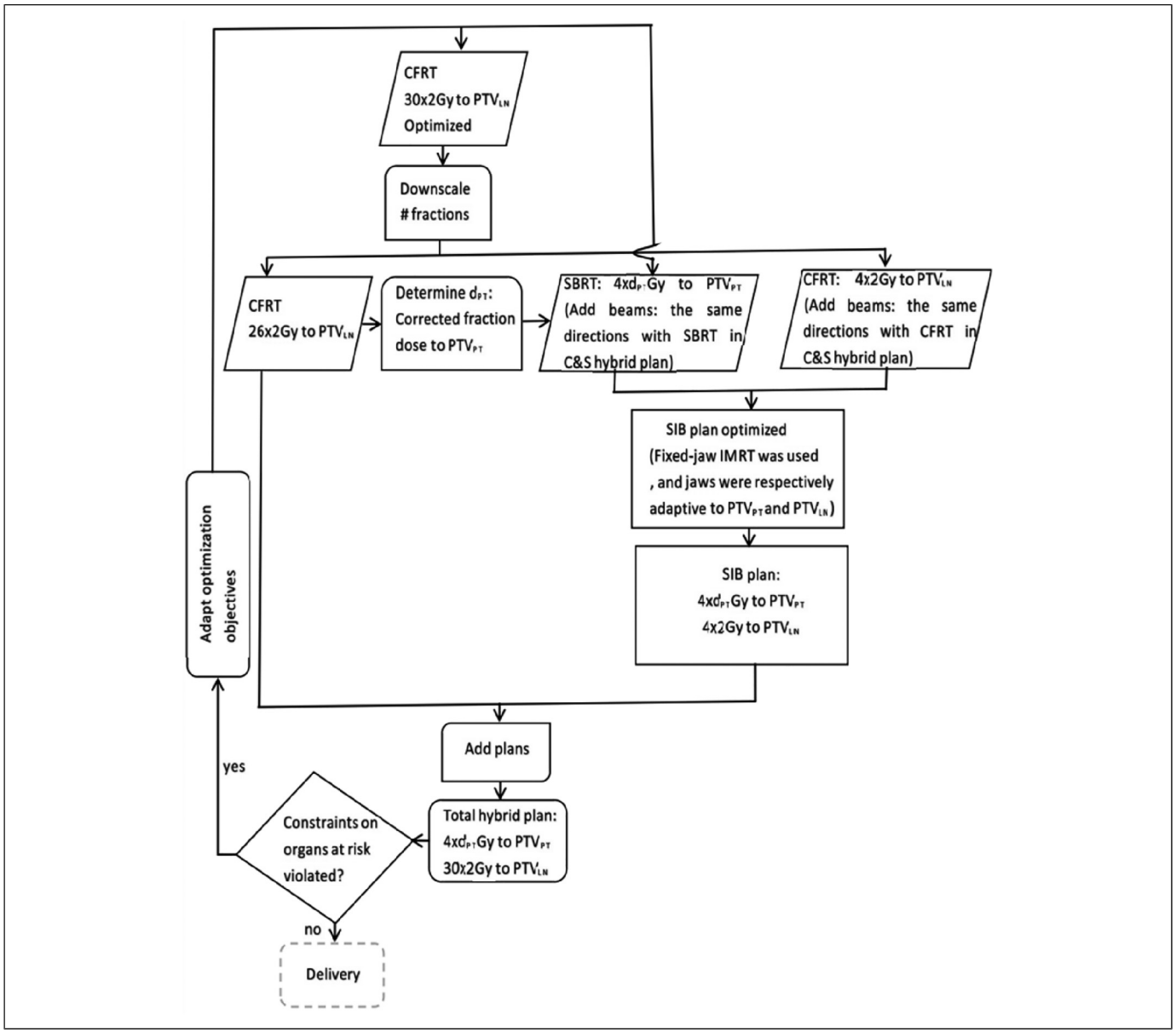

Figure 2. Flowchart of conventional fraction radiotherapy & simultaneous integrated boost (C & SIB) hybrid planning.

BED Plan Parameters

As a voxel dose of more than 8 Gy needed to be EQD_2 corrected in 4-fraction SBRT and SIB plans, an auxiliary contour structure called $Ring_{8Gy}$ (each voxel dose within $Ring_{8Gy}$ was more than 8 Gy) was, respectively, created for SBRT and SIB plans. Voxel-level EQD_2 dose within ITV and OARs covered by $Ring_{8Gy}$ was calculated by Equation (1)[33] with proper target and OARs α/β values (target 10, lung 3, spinal cord 2, esophagus 10, and heart 3)[34] and corrected by an in-house script using Matlab R2016a (The MathWorks Inc.), respectively, for SBRT and SIB plans, while voxel dose of OARs outside $Ring_{8Gy}$ remained the original. SBRT and SIB EQD_2 dose were, respectively, voxel-level superimposed with 30-fraction and 26-fraction CFRT plan dose to obtain BED plan parameters of C & S and C & SIB hybrid plans:

$$EQD_2 \text{voxel dose} = D \times (d + \alpha/\beta) / (2 + \alpha/\beta) \qquad (1)$$

where D is the voxel total dose (Gy); d is the voxel fraction dose (Gy), and the fraction number is 4.

BED plan parameters included: PTV_{PT} D_2, homogeneity index (HI), and CI_{140Gy}; PTV_{LN} D_2, HI, and CI_{60Gy}; total lung mean dose (MLD), V_5, and V_{20}; esophagus D_{max}, V_{35}, and V_{50}; heart mean dose (MHD), D_{max}, D_{30}, and D_5; spinal cord D_{max}.

CI_{140Gy} indicated the conformality index of PTV_{PT} covered by BED 140 Gy, which was estimated from the BED level at the border of PTV_{PT} with about 50 Gy physical dose using equation (1) and lung α/β value 3.

TCP/NTCP Parameters

To assess the clinical response difference between 2 kinds of hybrid plans, PT TCP (TCP_{PT}); LNs TCP (TCP_{LN}); total lung, esophagus, heart, and spinal cord NTCPs were, respectively, calculated using an in-house Matlab script. As tumor control events of PT and LNs were taken as 2 independent events in this work, total TCP (TCP_{total}) was taken as the product of TCP_{PT} and TCP_{LN}, and the EUD model was used for TCP calculation using the equations as follows[22,24–26]:

$$\mathrm{EUD} = \left[\sum_{i=1} (v_i D_i^{\alpha})\right]^{1/\alpha} \tag{2}$$

$$\mathrm{TCP} = \frac{1}{1 + (\mathrm{TCD}_{50} / \mathrm{EUD})^{4\gamma_{50}}} \tag{3}$$

where TCD_{50} means the uniform dose that was needed to control 50% of the tumor, γ_{50} means the TCP variation due to a 1% change of TCD_{50}, and D_i means a uniform dose of partial volume v_i. TCD_{50}, γ_{50}, and α were, respectively, set as 51.24 Gy, 0.83, and 0.30 for TCP calculation.[35]

Lyman–Kutcher–Burman model was adopted for NTCP calculation using the equations as follows[36]:

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \mathrm{e}^{-(x^2/2)\mathrm{d}x} \tag{4}$$

$$t = \frac{D_{\mathrm{eff}} - \mathrm{TD}_{50}}{\mathrm{mTD}_{50}} \tag{5}$$

$$D_{\mathrm{eff}} = \left(\sum_i v_i D_i^{1/n}\right)^n \tag{6}$$

where TD_{50}, n, and m were, respectively, set as 29.9 Gy, 1, and 0.41 for pneumonia from Semenko's results[37]; TD_{50}, n, and m were, respectively, set as 50.6 Gy, 0.64, and 0.13 for pericarditis from Martel's results[38]; TD_{50}, n, and m were, respectively, set as 51 Gy, 0.44, and 0.32 for esophagitis from Chapet's results[39]; TD_{50}, n, and m were, respectively, set as 66.5 Gy, 0.05, and 0.175 for myelitis from Luo et al's results.[40]

Hybrid planning method/TCD_{50}-specific TCPs

The LCR of cancer patients in a certain follow-up period depends on the individual tumor control possibility (TCP), and the TCP value is a hybrid planning method/TCD_{50} specific in hybrid radiotherapy for stage III NSCLC. In this work, PT and LNs TCP values of 20 patients with stage III NSCLC were, respectively, calculated to fully simulate LCR by involving different TCD_{50} and methods of hybrid planning. Equations (2) and (3) were used to calculate the TCP value. For each patient, PT and LNs TCPs were, respectively, calculated as a function of TCD_{50} ranging from 50 to 80 Gy at 1 Gy interval using an in-house Matlab script, and then the total TCP was obtained as the product of PT TCP and LNs TCP. Maximum, minimum, and averaged PT/LNs/total TCPs were, respectively, achieved from the TCP values of 20 patients with a certain TCD_{50} value ranging from 50 to 80 Gy at 1 Gy interval for 2 methods of hybrid planning. The hybrid planning method/TCD_{50}-specific TCPs were achieved to assess the PT/LNs/total TCPs of 20 NSCLC patients.

Delivery Accuracy of Hybrid Planning

The accuracy of hybrid plan delivery of 20 patients was, respectively, verified by a nontransit EPID dosimetry system (Varian). A gamma analysis was used for the comparison of planned and delivery dose distributions with a 5% dose threshold and a 2%/2 mm global gamma criterion for CFRT and SBRT plans, while a 2% dose threshold and a 2%/2 mm global gamma criterion for SIB plans. The delivery accuracy of hybrid plan components (CFRT, SBRT, and SIB) was acceptable in our center when the passing rates reached more than 90% using the above criteria. In this work, the verification results of hybrid plan components were analyzed, including that (1) % (γ<1) meant the gamma value passing rate; (2) γ_{mean} indicated the mean gamma value of all measured points; (3) % (area dose diff <3%) meant the area percentage relative to the whole region of interest where dose difference between measured and planned dose was <3%; and (4) ΔD_{isoc} (%) indicated the isocenter dose difference between planned and delivered doses.

Data Analysis

BED plan parameters and TCP/NTCP were analyzed by a paired-samples t-test between 2 methods of hybrid planning using SPSS 20.0 statistical software (IBM Corporation), and it was considered statistically when p-value <.05.

Results

BED Plan Parameters Comparison

For 20 patients' hybrid plans, target coverage (PTV_{PT}: $V_{100\%}$ ≥95%, PTV_{LN}: $V_{90\%}$ ≥99%) and OARs constraints were all met. BED isodose lines of 2 methods of hybrid planning were shown for 1 patient in Figure 3. Compared to C & S planning, PTV_{LN} achieved a higher dose conformability, spinal cord and esophagus got more sparing for the patient from C & SIB planning.

Figure 4 shows the BED-based dose-volume histograms (DVHs) of 2 methods of hybrid planning. The solid lines are indicated as averaged DVHs over a total of 20 patients for PTV_{PT} (red curve), PTV_{LN} (orange curve), total lung (blue curve), heart (magenta curve), esophagus (black curve), and spinal cord (green curve). The dashed lines show the upper and lower limits of the DVHs. In Figure 4, it could be seen that C & SIB plans are close to each other with respect to irradiation of PTV_{LN}, while D_2 values of PTV_{LN} from C & SIB plans were statistically lower than the ones from C & S plans.

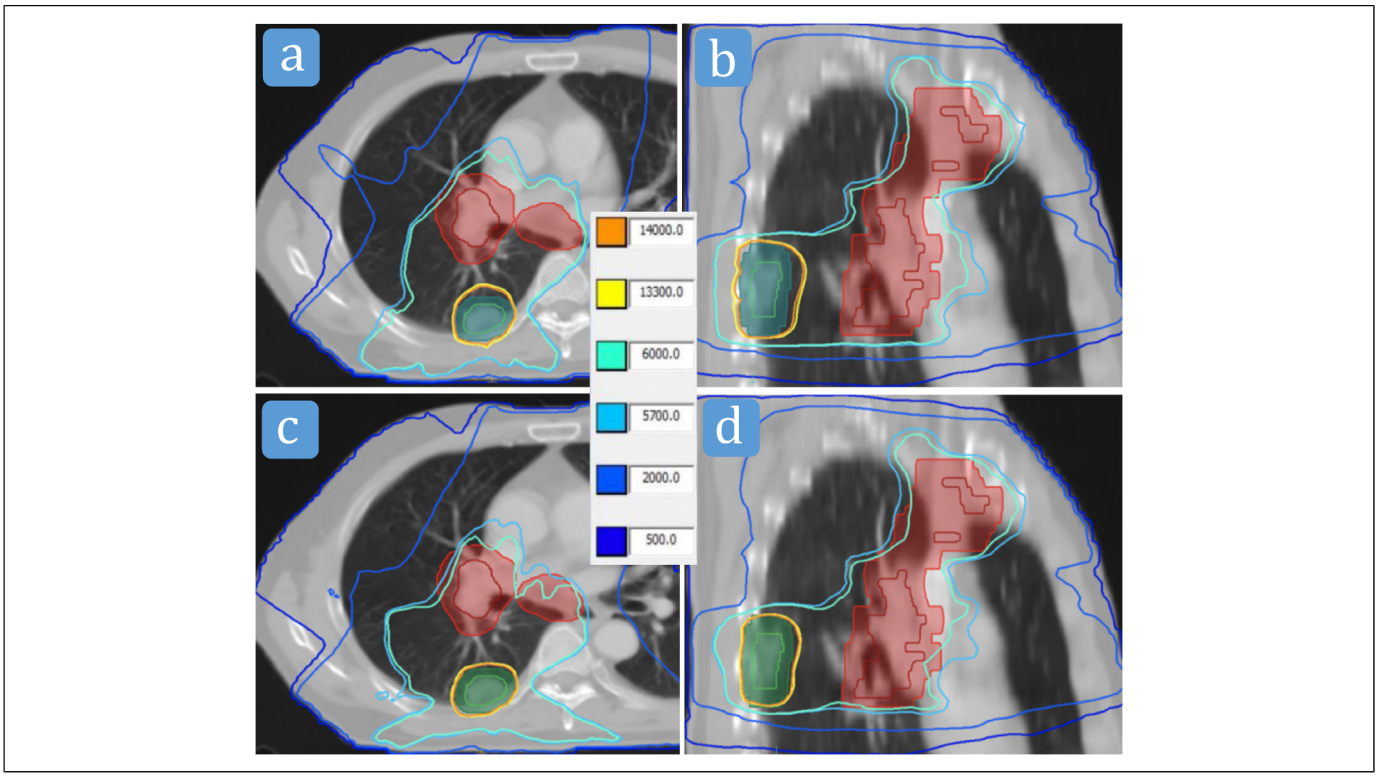

Figure 3. BED isodose lines of one patient's C & S plan were shown in axial (a) and coronal view (c). For comparison, BED isodose lines of the corresponding C & SIB plan were shown in axial view (b) and sagittal view (d). The absolute BED values were given in the legend as: 13 000 cGy (brown), 6800 cGy (yellow), 6000 cGy (green), 4500 cGy (dark green), 2000 cGy (blue), and 500 cGy (dark blue). α/β values: target 10, lung 3, spinal cord 2, esophagus 10, and heart 3.
Abbreviations: BED, biological equivalent dose; CFRT, conventional fraction radiotherapy; SBRT, stereotactic body radiotherapy; SIB, simultaneous integrated boost; C & S, CFRT and SBRT; C & SIB, CFRT and SIB.
Bold values in Table 2 indicate that the groups of data have statistical difference.

The esophagus DVHs have a larger deviation due to the difference in anatomical morphology over a total of 20 patients.

The averaged BED plan parameters of 20 patients are, respectively, shown for 2 kinds of hybrid plans in Table 2. The results are shown as mean values and standard deviations. Irradiation of 95% volume of PT resulted in comparable BED values close to 140 Gy, while the BED value of LNs disease was close to 60 Gy. C & SIB hybrid planning provided lower irradiation levels of the esophagus (V_{50} and D_{max}) and spinal cord (D_{max}) compared to C & S planning, while a lower-dose hotspot (D_2) was observed in PTV_{LN} from C & SIB planning.

TCP/NTCP Comparison

In Table 3, the TCP/NTCP results demonstrate that both methods of hybrid planning are effective techniques for irradiation of stage III NSCLC. Most of the TCP/NTCP results were equivalent between the 2 methods of hybrid plans, while C & SIB planning provided lower esophagus NTCP (43.2 ± 22.4%) compared to C & S planning (45.8 ± 23.6%).

Hybrid Planning and TCD_{50}-Specific TCPs

The averaged results of PT/LNs/total TCP values and their Max/Min limits are shown in Figure 5 as a function of TCD_{50} for 2 methods of hybrid planning. According to Mehta et al[27] and Wulf et al,[28] the TCD_{50} values probably lie in a range from 50 to 80 Gy. In this case, averaged TCP curves show that C & S and C & SIB planning should have almost equivalent efficiency. In general, C & S plans to allow irradiation of the PT and LNs to a higher dose than C & SIB plans, and it is observed that averaged PT/LNs/total TCP curves as a function of TCD_{50} are slightly higher for C & S planning in Figure 5(a) to (c). Meanwhile, Figure 5 shows that the gaps between Max and Min limits of LNs/total TCP curves are closer for C & SIB planning, which may indicate that the robustness of LNs/total TCPs achieved by C & SIB planning would be better.

The hybrid planning method/TCD_{50}-specific LNs/PT/total TCPs are, respectively, shown in Figure 6(a) to (c) for 20 NSCLC patients. PT/LNs/total TCPs decrease (green→red) with a higher TCD_{50} ranging from 50 to 80 Gy for 2 methods of hybrid planning. Total TCPs are mainly determined by lower LNs TCPs (ranging from 30% to 79%) which are

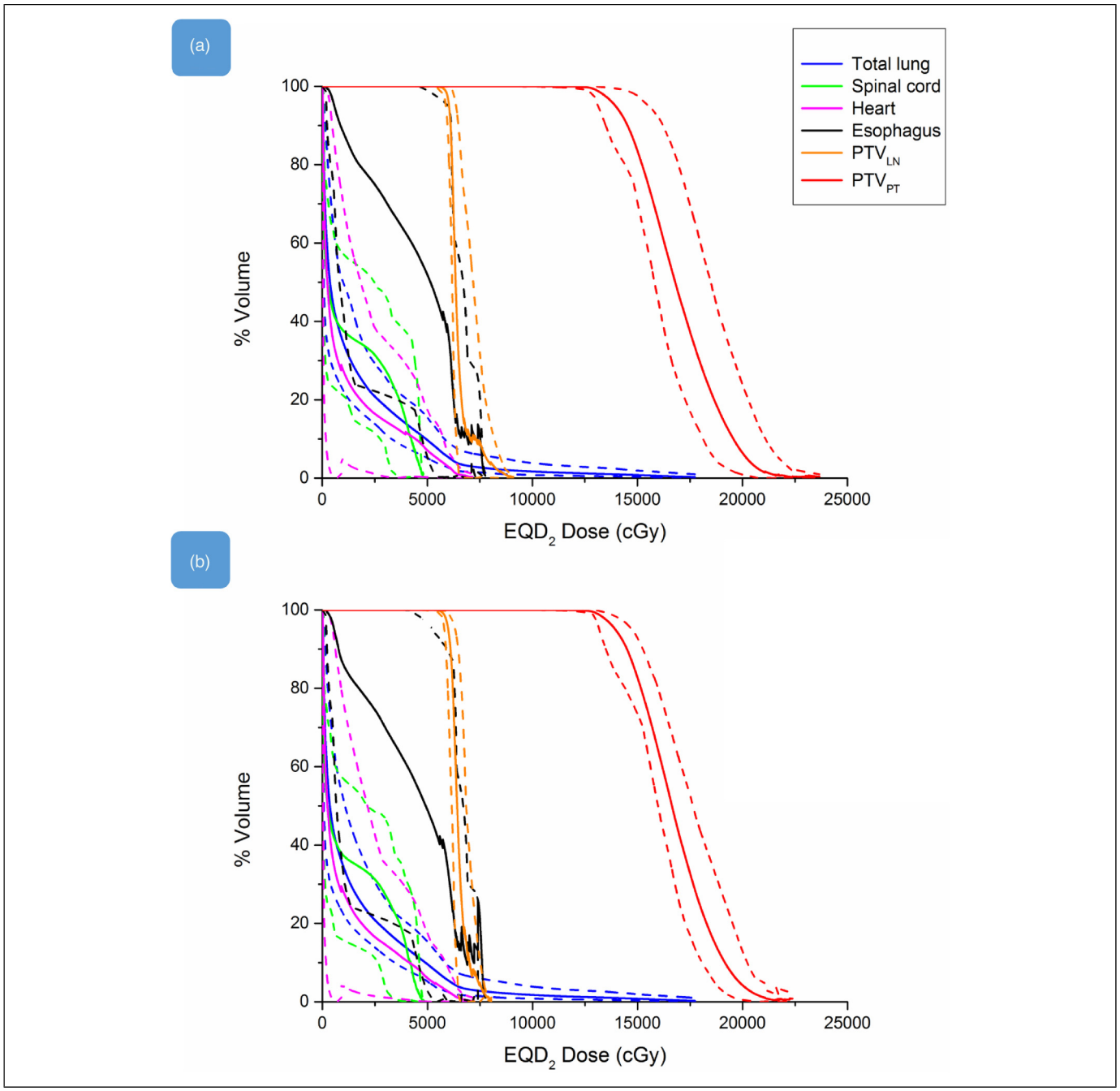

Figure 4. BED-based dose-volume histograms for C & S plans (a) and C & SIB plans (b). Solid curves show average values and dashed curves show Max/Min values. Red curve: PTV_{PT}, orange curve: PTV_{LN}, blue curve: total lung, green curve: spinal cord, magenta curve: heart, and black curve: esophagus.

Abbreviations: BED, biological equivalent dose; CFRT, conventional fraction radiotherapy; SBRT, stereotactic body radiotherapy; SIB, simultaneous integrated boost; C & S, CFRT and SBRT; C & SIB, CFRT and SIB; PTV_{PT}, planning target volume of the primary tumor; PTV_{LN}, planning target volume of the lymph node.

irradiated by CFRT, compared to PT with TCP values of more than 91%, which are irradiated by SBRT.

Delivery Accuracy of Hybrid Plans Components

Table 4 summarizes portal dosimetry results of the hybrid plan components (SBRT, CFRT, and SIB plans). Mean results and ranges of 20 patients were given, including passing rates (% [$\gamma<1$]), mean γ value (γ_{mean}), the area percentage of dose difference <3% (% [area dose diff <3%]), and dose difference at isocenter (ΔD_{isoc} [%]).

The average passing rates of SBRT and CFRT plans were around 97%, while SIB plans reached about 99% using the 2%/2 mm criterion. The delivery errors of hybrid plan

Table 2. BED Plan Parameters Comparison Between Two Methods of Hybrid Planning

	α/β	Parameter	C & S	C & SIB	*P*-value
PTV_{PT}	10	D_2	204.4 ± 8.0	204.7 ± 10.4	.891
		HI	1.40 ± 0.08	1.41 ± 0.07	.880
		CI_{140Gy}	0.77 ± 0.10	0.80 ± 0.10	.208
PTV_{LN}	10	**D_2**	**74.8 ± 10.6**	**69.8 ± 3.7**	**.038**
		HI	1.20 ± 0.14	1.14 ± 0.05	.055
		CI_{60Gy}	0.38 ± 0.13	0.37 ± 0.13	.193
Total lung	3	V_5	46.0 ± 11.2	44.6 ± 11.7	.260
		V_{20}	25.4 ± 7.9	24.1 ± 5.7	.333
		MLD	15.7 ± 3.1	15.4 ± 3.1	.280
Heart	3	D_5	38.5 ± 22.7	37.6 ± 22.5	.365
		D_{30}	12.2 ± 12.7	11.8 ± 12.6	.284
		D_{max}	66.7 ± 17.1	63.5 ± 21.6	.466
		MHD	10.7 ± 7.6	10.5 ± 7.6	.408
Esophagus	10	V_{35}	66.3 ± 22.8	61.7 ± 23.9	.238
		V_{50}	**52.1 ± 27.4**	**49.6 ± 27.9**	**.026**
		D_{max}	**68.8 ± 6.9**	**66.3 ± 5.7**	**.039**
Spinal cord	2	**D_{max}**	**46.6 ± 5.4**	**45.0 ± 5.3**	**.027**

Abbreviations: BED, biological equivalent dose; SIB, simultaneous integrated boost; PTV_{PT}, planning target volume of the primary tumor; PTV_{LN}, planning target volume of lymph node; MHD, heart mean dose; MLD, lung mean dose.
Bold values in Table 2 indicate that the groups of data have statistical difference.

Table 3. TCP/NTCP Comparisons Between Two Methods of Hybrid Planning.

Parameters	C & S (mean ± Std)	C & SIB (mean ± Std)	*P*-value
TCP_{LN}	68.6 ± 3.1%	68.4 ± 2.1%	.719
TCP_{PT}	98.1 ± 0.3%	98.0 ± 0.2%	.395
TCP_{total}	67.3 ± 3.1%	67.1 ± 2.0%	.670
$NTCP_{total\ lung}$	9.1 ± 4.4%	9.3 ± 5.2%	.583
$NTCP_{heart}$	0.000 ± 0.006%	0.000 ± 0.01%	.291
$NTCP_{eso}$	**45.8 ± 23.6%**	**43.2 ± 22.4%**	**.034**
$NTCP_{spinal\ cord}$	1.1 ± 0.7%	0.9 ± 0.6%	.086

Abbreviations: TCP, tumor control probability; NTCP, normal tissue complication probability; SIB, simultaneous integrated boost; LN, lymph node; PT, primary tumor; CFRT, conventional fraction radiotherapy; SBRT, stereotactic body radiotherapy; C & S, CFRT and SBRT; C & SIB, CFRT and SIB; TCP_{LN}, LNs TCP; TCP_{total}, total TCP.
Bold values in Table 3 indicate that the groups of data have statistical difference.

components were acceptable in our center when the passing rates were more than 90%. The γ_{mean} of all plans was no more than 0.46 which indicated great consistency between planned and measured doses. Figure 7 shows an example of composite dose difference. Average percentage (area dose diff <3%) of SBRT and CFRT plans were, respectively, 74.4% and 78.7%, while SIB plans reached about 94.5%. The measured dose at the isocenter of the hybrid plans showed about 2% systematically lower than the planned dose.

Discussion

Two methods of IMRT-based hybrid planning were used in the dosimetric and radiobiological study of stage III NSCLC. BED plan parameters and TCP/NTCP showed that 2 methods of hybrid planning were feasible and did not compromise OARs' dose constraints. For a fair comparison, dose regime 4 × 12.5Gy was given to PT for all hybrid plans in this hybrid planning study. Lower D_2 and HI of PTV_{LN} resulted in slightly lower averaged LNs/total TCP curves for C & SIB planning. Closer Max/Min LNs and total TCP curves indicated better robustness of LNs and total TCPs for C & SIB planning. C & SIB planning could spare the esophagus and spinal cord more in BED dosimetry, and a lower esophagus NTCP could be achieved by C & SIB planning. The Hybrid planning method/TCD_{50}-specific TCPs were also evaluated for 20 stage III NSCLC patients. The dose verification results of the subplans involved in the 2 kinds of hybrid plans were very good, which showed that 2 methods of hybrid planning could be delivered accurately in our center.

As the nodal area always is involved in most regional recurrences for stage III NSCLC treated by CFRT,[15,16] it is important to reduce the risk of LN recurrence. The tolerance of CCRT followed by a sequential SBRT boost in stage III NSCLC has been reported by several studies.[4–7] BED ≥100 Gy has been adopted by all these studies to obtain a high LCR. Most of these studies applied a dose escalation to both PT and LNs residual disease,[4–7] while grade 5 bronchopulmonary hemorrhage and

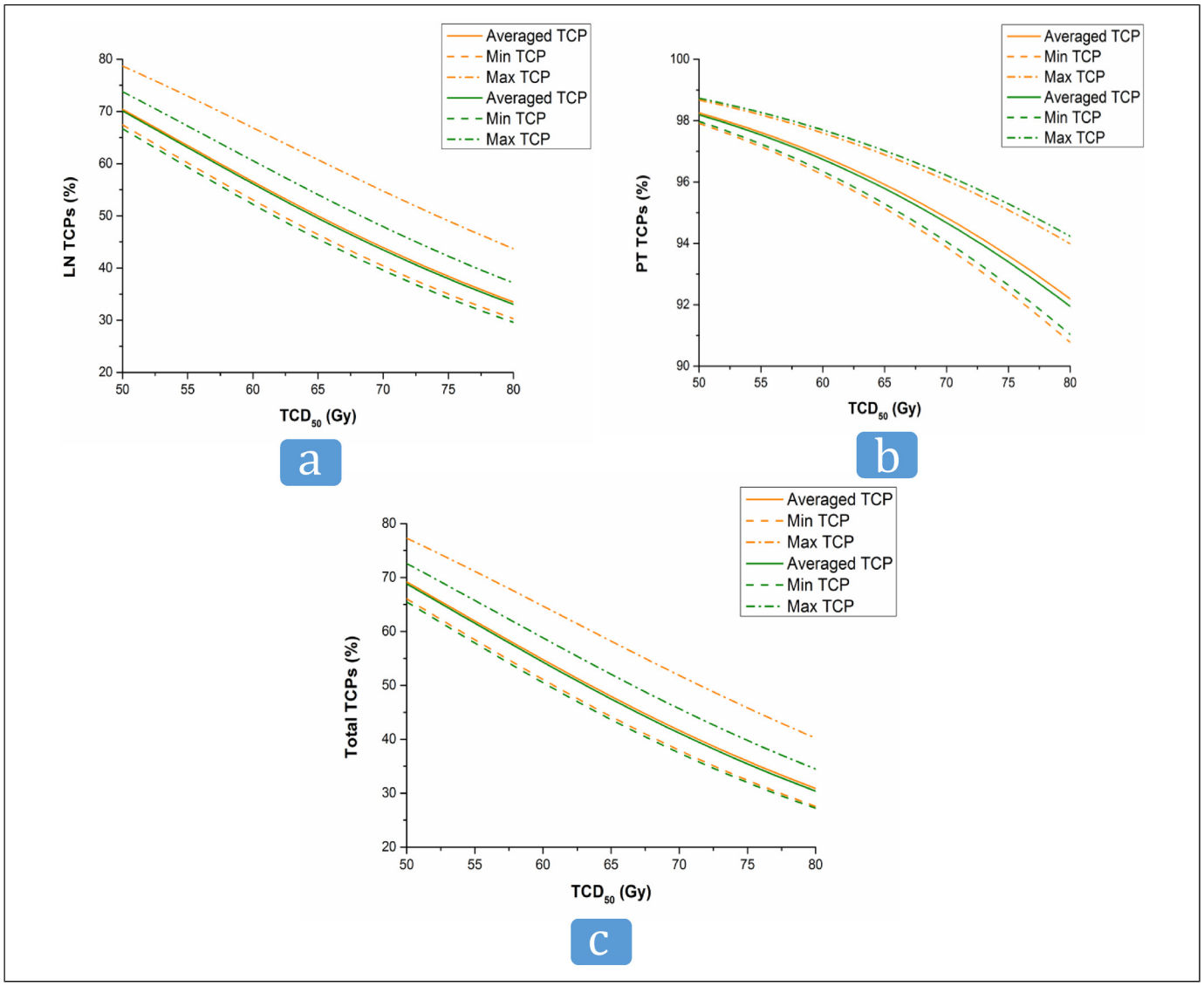

Figure 5. The averaged dependence (solid line) of LNs TCP (a), PT TCP (b), and total TCP (c) on TCD_{50} for C & S planning (brown line) and C & SIB planning (green line). Dashed lines show the lower and upper limits.
Abbreviations: LN, lymph node; PT, primary tumor; SIB, simultaneous integrated boost; TCD50, radiation dose needed to control 50% of tumor; TCP, tumor control probability;

a tracheoesophageal fistula were consequently observed.[5,6] The Radiation Therapy Oncology Group (RTOG) 0617 trial, which analyzed the treatment response difference between groups that received a total dose of 74 and 60 Gy by 2 Gy per fraction, found that 2-year local recurrence free survival and overall survival rates did not increase with a higher total dose.[8] This justifies an appropriate dose regime for LNs combined with an SBRT dose escalation only to the PT, thus high BED irradiation to mediastinal organs (eg, heart and esophagus) is avoided, which often reduces the risk of cardiac and esophageal toxic events in both CFRT as SBRT[8–11] and possibly reduces an adverse effect on overall survival rates.[8,12,13]

In this work, we chose 2 methods of hybrid planning with dose escalation only to PT. C & S hybrid planning has simple steps, but it may lead to obvious interaction effects when the lung lesions are close to the LNs disease. C & SIB hybrid planning is relatively more complex, but the SIB plan component may reduce the total interaction effect to a certain extent. Due to the differences in the methods between the 2 hybrid plans, it may cause differences in BED plan parameters, and may further result in clinical response differences for stage III NSCLC.

There have been few studies to compare 2 kinds of recently widely used hybrid plans for stage III NSCLC to our knowledge. On account of the assumption that the proper BED calculation model[33] and target & OARs' α/β values[34] have been used for the results of SBRT and SIB plans, it is the first research to evaluate the comparative advantages of two methods of IMRT-based hybrid planning based on BED plan parameters and TCP/NTCP. In general, the question arises whether the

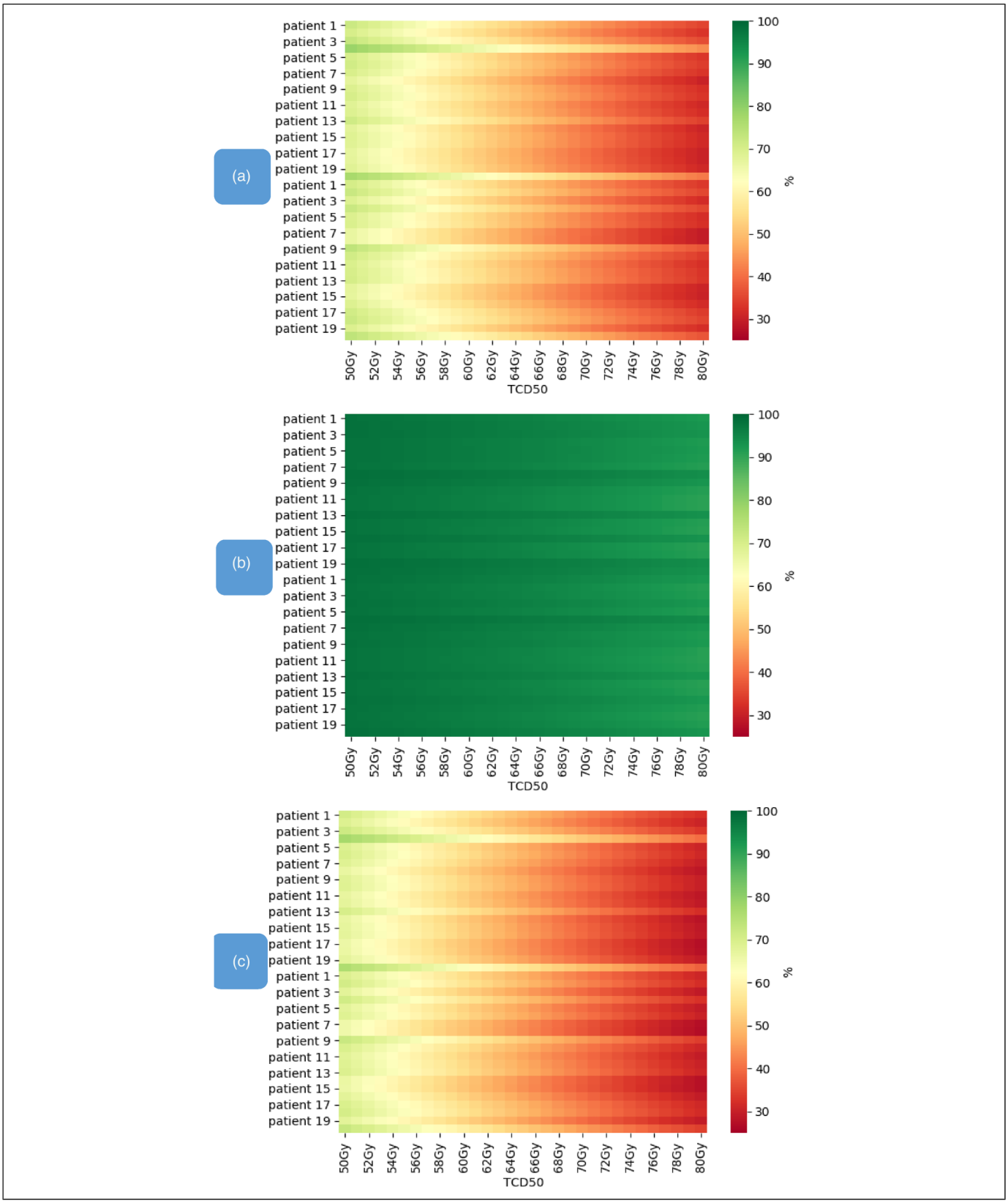

Figure 6. LNs TCPs (a), PT TCPs (b), and total TCPs (c) were plotted in (a, b, and c) as a function of TCD_{50} ranging from 50 to 80 Gy at 1 Gy interval for 20 NSCLC patients. First/second 20 patients' TCPs were, respectively, achieved from C & S and C & SIB planning.
Abbreviations: LN, lymph node; NSCLC, nonsmall cell lung cancer; PT, primary tumor; TCD_{50}, radiation dose needed to control 50% of tumor; TCP, tumor control probability.

Table 4. QA Results of the Hybrid Plan Components.

	SBRT plans	CFRT plans	SIB plans
% (γ<1)	97.9 (96.2-99.2)	97.5 (89.6-100)	99.4 (97.6-100)
γ_{mean}	0.29 (0.23-0.39)	0.31 (0.22-0.46)	0.16 (0.14-0.21)
% (Area dose diff <3%)	74.4 (22.6-90.8)	78.7 (23.1-91.3)	94.5 (91.5-97.6)
ΔD_{isoc} (%)	−2.1 (−6.9 to −0.2)	−1.7 (−8.5 to 6.5)	−1.6 (−3.9 to 0.1)

Abbreviations: QA, quality assurance; SBRT, stereotactic body radiotherapy; CFRT, conventional fraction radiotherapy; SIB, simultaneous integrated boost.

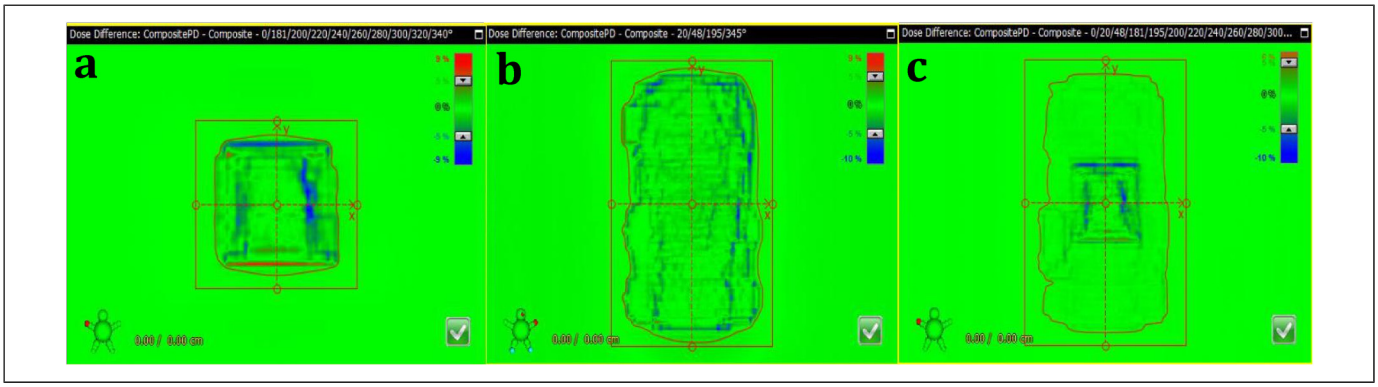

Figure 7. Dose difference map of composite beams of one patient's hybrid plan components (SBRT plan [a], CFRT plan [b], and SIB plan [c]) in nontransit portal dosimetry measurements.
Abbreviations: SBRT, stereotactic body radiotherapy; CFRT, conventional fraction radiotherapy; SIB, simultaneous integrated boost.

comparison of the 2 hybrid plans is at all justified by the uncertainty of the planning evaluation due to unsafe α/β assumptions. From our previous work,[41] it could be seen that there were at least moderate correlations between physical and BED plan parameters if the same BED calculated model and α/β assumptions were used for 2 methods of hybrid planning. Under the same conditions, the results of the comparison between the 2 hybrid plans still seem to be credible in this work.

As the presence of the difference between 2 time-point planning CTs and related anatomical morphology, the sum of hybrid plans was even more difficult, especially for the 3 patients treated by CFRT with a sequential SBRT boost. All hybrid plans were retrospectively completed on first planning 4D-CT due to the reason that we tried to compare BED plan parameters and TCP/NTCP of 2 hybrid plans, while the differences in anatomical structure between the 2 planning CTs were neglected in this study.

The interplay effect in relation to moving targets still needed to be considered to improve the robustness of dose distribution, and 2 kinds of IMRT-based hybrid planning were proposed in this work. Jens et al[42] reported that robust treatment sequences correlated with human breathing patterns could be produced by iteratively reducing the maximum allowed dose rate with the application of fast IMRT/volumetric modulated arc therapy (VMAT) delivery techniques. Damodar et al[43] reported a simple d-VMAT-based SBRT technique, and it could potentially reduce multileaf collimator (MLC) interplay effects with less MLC modulation through the target and dosimetric errors from small fields. IMRT-based SBRT planning with modulated single-segment fields was used in this work, and it was proposed in our previous work.[32] The resulting dose distribution may be robust to possible interplay effects that are known from highly modulated IMRT irradiations and high-dose rates in relation to moving targets.

SBRT combined with CFRT has been adopted in treatments of patients with locally advanced cancers.[6,16] The feasibility of SBRT (total dose 40-60 Gy was used in 4 fractions) followed by CFRT (total dose 66 Gy was adopted in 30 fractions for NSCLC and 52.5 Gy in 25 fractions was used for small cell lung cancer) has been evaluated for patients with stage III lung cancer by a prospective single-institution study.[16] About 76% crude LCR was achieved during a 5-year follow up, which was higher than our calculated result (67.3%) by C & S hybrid planning with a similar dose regime to PT combined with a lower dose regime to LNs (total of 60 Gy, 2 Gy/fraction).

Another prospective study[6] evaluated the treatment response by SBRT boost in both residual lung and LNs disease after concomitant chemoradiotherapy for unresectable stage III NSCLC. The rate of local-regional control at 3 years was 59% with a cumulative BED 112.3 Gy to residual lung and LNs disease. More trials are needed to make clear whether implementation of SBRT to both residual lung lesions and LNs decreases the risk of nodal in-field recurrences compared to SBRT to PT followed by CFRT to LNs.

As the interaction effect was reduced by C & SIB planning compared to C & S planning, the physical plan parameter of PTV_{LN} CI benefited from C & SIB planning (0.56 ± 0.12) compared to C & S planning (0.52 ± 0.11) ($p = .004$).

Although there was no statistical difference between C & SIB and C & S planning for the BED plan parameters such as PTV_{LN} CI, which may be justified by BED recalculation (a nonlinear BED model).[33] BED plan parameters of PTV_{LN} D_2 and HI were significantly lower by C & SIB planning, resulting that averaged LNs/total TCP curves were slightly lower as a function of TCD_{50} by C & SIB planning, meanwhile, the robustness of LNs/total TCPs has improved with closer Max/Min TCP curves by C & SIB planning.

The incidence rate of grade ≥3 acute radiation pneumonitis (RP) for patients who received SBRT boost before/after chemoradiation in lung cancers were, respectively, 21% (4 of 21) by Yeon et al,[16] 11.4% (4 of 35) by Feddock et al,[4] while the incidence rate of grade ≥2 acute RP was 25% (4 of 16) by Karam et al.[7] Our calculated lung NTCP values, 9.1 ± 4.4% for C & S plans and 9.3 ± 5.2% for C & SIB plans, were similar to, even less than the RP possibilities from the above 3 results, which may be due to the reason that dose regimes used in above studies were different, meanwhile, patients characteristics, such as age in years and smoking history, are predictive factors for RP,[44,45] and there may be some differences in the patient characteristics between the studies.

Lung constraints in this work included MLD <20 Gy, V5 <60%, and V20 <30%. The relevance of lung volume dose with the rate of RP grade ≥3 was evaluated by a study,[45] indicating that the rate of RP grade ≥3 was only 2% when the lung dose threshold was met, defined by V50 ≤10%, V35 ≤15%, V25 ≤20%, and V20 ≤25%. Stricter lung constraints are therefore needed for active smoking and/or old-aged patients, and those with poor lung function.

Compared to our calculated median esophagus NTCP of 45.8% by C & S planning, similar acute esophagitis (9 of 21, 42.9%) was observed by Yeon et al[16] with a slightly higher dose regime than LNs. A higher possibility of Grade 1 or 2 radiation esophagitis (11 of 15, 73.3%) was reported by Higgins et al,[6] which indicated that more trials are needed to make clear whether implementation of SBRT to both residual lung and LNs disease decreases the risk of nodal in-field recurrences, while improves the risk of acute esophagitis with a low grade. In this work, BED plan parameters of esophagus V_{50} and D_{max} of C & SIB plans were lower than those of C & S plans, and a significantly lower calculated esophagus NTCP was observed by C & SIB planning. A puzzling problem has arisen that as the esophagus is an early response tissue, a lower esophagus NTCP achieved by C & SIB planning may be compromised by nearly 1 week shorter OTT by C & SIB irradiation compared to C & S irradiation.

There was little follow-up data on the risk of pericarditis and myelitis from stage III lung cancer patients treated by hybrid planning, except the result from Feddock et al[4] that no patients with pericarditis were observed. In this study, although the probabilities of pericarditis and myelitis calculated based on NTCP models were very low, we still need to be cautious about the individual risk of stage III NSCLC patients.

TCP/NTCP of stage III NSCLC is a hybrid planning method, dose regime, and TCD_{50}/TD_{50} specific. At present, the dose regime of lung SBRT has been chosen mainly according to AAPM/RTOG reports.[46–50] Individual dose regime for SBRT treatment has still been a challenge. Meanwhile, similar to TD_{50}, the radiation dose needed to control 50% of tumor (TCD_{50}) is different among individuals,[27,28] due to the difference in radiosensitivity between tumor individuals. In this work, It is investigated that tumors with different TCD_{50} levels could obtain different TCPs under the same irradiation level. This work provides a preliminary exploration of the process of taking TCD_{50}/TD_{50} as a variable in a TCP/NTCP-objective optimization, but it still depends on a deeper understanding of the radiobiological behavior of tumors and OARs. In the context of reliable TCP/NTCP models and correct TCD_{50}/TD_{50} values, this work has the potential to be used to optimize the selection of the hybrid planning method and dose regime for stage III NSCLC in a TCP/NTCP-objective optimization.

EPID dosimetry has been widely used in the pretreatment dose verification of CFRT and SBRT.[51,52] In this study, nontransit EPID dosimetry was used to verify the components involved in the 2 kinds of hybrid plans, and the results passed the criteria of our center. The average passing rate percentage (γ<1) (2%, 2 mm) was higher than 97.5%, the average of γ_{mean} was <0.31, and the mean value of ΔD_{isoc} (%) was no more than 2.1% for all the components. No patient positioning and anatomical errors in nontransit EPID dosimetry dose verification may result in good pass rates, and they were generally better than the transit results.[52] As the measured dose image of the SIB plan included 2 areas in imaging: PTV_{PT}-related high-dose area and PTV_{LN}-related low-dose area, we set the dose threshold as 2% to include the low-dose area in the analysis range. Since the global maximum dose normalization method is adopted in the calculation of gamma value, most gamma values in the low-dose area of SIB plans are <1, which makes them the highest passing rates among the components of hybrid plans (99.4% [97.6%-100%]).

The study presented is a retrospective planning study over 20 patients whose PT is located inside the lung PTV_{PT}, and PET-positive LNs located in the mediastinal area are defined as PTV_{LN}. The hybrid plans require that PTV_{PT} and PTV_{LN} are relatively small in volume and spatially separated from each other, only approximately 5%-10% of patients are suitable for hybrid planning. This significantly limits the number of stage III NSCLC as candidates for the presented hybrid plans, and the number would likely increase in the case of an SBRT dose regime with more fractions. This work remains a retrospective comparative planning study. Meanwhile, it is still not clear about individual TCD_{50} values for the specific lung cancer patients, and a reliable TCP/NTCP calculation model suitable for patients treated by hybrid radiotherapy have not yet been established.

In conclusion, CFRT & SIB planning has more advantages on BED plan parameters and TCP/NTCP than CFRT & SBRT planning. Both methods of IMRT-based hybrid planning could be executed accurately for stage III NSCLC. The effectiveness of the results needs to be validated in the hybrid trial.

Authors' Contributions

HW and YKZ: data collection, statistical analysis, writing, and revising the manuscript. YH, HC, YS, YHD, AHF, HLG, and XRM: statistical analysis and revising the manuscript. QK and XZY: study design and critical revision of the manuscript. All authors gave final approval for the version to be published.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval and Consent to Participate

Project name: Promotion and management of stereotactic radiotherapy for lung cancer based on the internet. The study is a retrospective study. When the study began, all selected patients signed informed consent and completed radiotherapy. Ethical standards and patients' confidentiality were ensured and in line with regulations of the local institutional review board and data safety laws. This study was approved by the Ethics Committee of Shanghai Chest Hospital (the committee's reference Number: KS1863).

Consent for Publication

Not applicable.

Availability of Supporting Data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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