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Regression models for predicting physical and EQD₂ plan parameters of two methods of hybrid planning for stage III NSCLC

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Abstract

Background/purpose: To establish regression models of physical and equivalent dose in 2 Gy per fraction (EQD₂) plan parameters of two kinds of hybrid planning for stage III NSCLC.

Methods: Two kinds of hybrid plans named conventional fraction radiotherapy & stereotactic body radiotherapy (C&S) and conventional fraction radiotherapy & simultaneous integrated boost (C&SIB) were retrospectively made for 20 patients with stage III NSCLC. Prescription dose of C&S plans was 2 Gy × 30f for planning target volume of lymph node (PTV_{LN}) and 12.5 Gy × 4f for planning target volume of primary tumor (PTV_{PT}), while prescription dose of C&SIB plans was 2 Gy × 26f for PTV_{LN} and sequential 2 Gy × 4f for PTV_{LN} combined with 12.5 Gy × 4f for PTV_{PT}. Regression models of physical and EQD₂ plan parameters were established based on anatomical geometry features for two kinds of hybrid plans. The features were mainly characterized by volume ratio, min distance and overlapping slices thickness of two structures. The possibilities of regression models of EQD₂ plan parameters were verified by spearman's correlation coefficients between physical and EQD₂ plan parameters, and the influence on the consistence of fitting goodness between physical and EQD₂ models was investigated by the correlations between physical and EQD₂ plan parameters. Finally, physical and EQD₂ models predictions were compared with plan parameters for two new patients.

Results: Physical and EQD₂ plan parameters of PTV_{LN} Cl_{60Gy} have shown strong positive correlations with PTV_{LN} volume and min distance_(PT to LN), and strong negative correlations with PTV_{PT} volume for two kinds of hybrid plans. PTV_(PT+LN) Cl_{60Gy} is not only correlated with above three geometry features, but also negatively correlated with overlapping slices thickness_(PT and LN). When neck lymph node metastasis was excluded from PTV_{LN} volume, physical and EQD₂ total lung V₂₀ showed a high linear correlation with corrected volume ratio_(LN to total lung). Meanwhile, physical total lung mean dose (MLD) had a high linear correlation with corrected volume ratio_(LN to total lung), while EQD₂ total lung MLD was not only affected by corrected volume ratio_(LN to total lung) but also volume ratio_(PT to total lung). Heart D₅, D₃₀ and mean dose (MHD) would be more susceptible to overlapping structure_(heart and LN). Min distance_(PT to ESO) may be an important feature for predicting EQD₂ esophageal max dose for hybrid plans. It's feasible for regression models of EQD₂ plan parameters, and the consistence of the fitting goodness of physical and EQD₂ models had a positive correlation with spearman's correlation coefficients between physical and EQD₂ plan parameters. For total lung V₂₀,

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ipsilateral lung V_{20} , and ipsilateral lung MLD, the models could predict that C&SIB plans were higher than C&S plans for two new patients.

Conclusion: The regression models of physical and EQD₂ plan parameters were established with at least moderate fitting goodness in this work, and the models have a potential to predict physical and EQD₂ plan parameters for two kinds of hybrid planning.

Keywords: Physical plan parameter, EQD₂ plan parameter, Regression model, Hybrid planning, Stage III NSCLC

Background

Definitive concurrent chemoradiotherapy (CCRT) has been recommended as the standard treatment for unresectable or medically inoperable stage III non-small cell lung cancer (NSCLC) [1–3]. Primary tumor (PT) and lymph node metastasis (LN) are treated by conventional fraction radiotherapy (CFRT) for these patients.

Two studies did a detailed analysis about locoregional failure in stage III NSCLC treated by CFRT, and showed that PT recurrence occurred more often than LN recurrence [4, 5]. Therefore, there is a rationale for PT dose escalation. The results of the CHISEL trial [6] suggested that implement of stereotactic body radiotherapy (SBRT) to PT and CFRT to LN could improve control of PT and further improve control of the entire region with two distinct target volumes. SBRT is suitable for PT dose escalation as there is a certain distance between PT and LN which could allow for dose drop. Meanwhile, Tighter margin of planning target volume (PTV) and steeper dose drop around PT could reduce the risk of toxicity events while accurate dose delivery to PT could be implemented.

It has been reported that two main methods for hybrid planning with different dose regimes could be used to PT and LN. First method has now been tried in clinic that implement CFRT before [7–10] or after [11] SBRT boost for LN and PT (called C&S plan). Second method was proposed by Peulen et al. [12] that LN was treated by partial fractions of CFRT, and then simultaneous integrated boost (SIB) was implemented for PT and LN (called C&SIB plan).

Both methods of hybrid planning may be challenging, because the dose conformability is affected by the dose superposition of the two sub-plans. The closer distance between PT and LN results in more significant interaction effect, which makes equivalent dose in 2 Gy per fraction (EQD₂) evaluation of the hybrid plan more complicated. It seems more meaningful to evaluate the hybrid plan when EQD₂ corrected dose of SBRT/SIB plan is superposed with the dose of CFRT plan. In addition, anatomical geometry features may compromise the optimization objectives of two steps of hybrid planning, which greatly increases the difficulty of step-by-step optimization and evaluation. The features are mainly

characterized by volume ratio of two contour structures, minimum distance between two structures, overlapping slices thickness of two spatially separated structures, and the volume ratio of overlapping structure by two structures to one of them.

Although these methods of hybrid planning may provide more opportunities to stage III NSCLC CCRT, it's still not very clear which kind of hybrid planning has more dosimetric advantages, especially EQD₂ dose advantages when the patients have different anatomical geometry features. Meanwhile, it would be challenging to compare EQD₂ plan parameters of different kinds of hybrid plans in clinical practice. To say the least, it would be time-consuming to complete different kinds of hybrid plans for comparison. In this work, multiple regression models based on anatomical geometry features were proposed to predict plan parameters of two kinds of hybrid planning, which was a meaningful attempt to solve the above problems.

Materials and methods

Patient selection

A total of 20 patients with stage III NSCLC from January 2016 to June 2020 were retrospectively selected in our center, including 18 male patients and 2 female patients. Three patients received concurrent chemoradiation with CFRT for LN before SBRT boost for PT, as superior vena cava was oppressed by enlarged mediastinal lymph nodes, while the other seventeen patients received SBRT boost for PT before concurrent chemoradiation with CFRT for LN. Mean PTV_{PT} volume is 30.7 cc (10.9–100.1 cc), and mean PTV_{LN} volume is 199.5 cc (24.8–452.3 cc). Table 1 summarizes patients characteristics and anatomical geometry features. Anatomical geometry features were shown on CT and digitally reconstructed radiograph (DRR) images (Fig. 1).

Treatment preparation

Each patient was fixed using a thermoplastic mask, and a 4D-planning CT scan ranged from the neck to the lower edge of the liver, including the entire lung, with 3-mm thickness was acquired. 10 respiratory phases CT images

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	3
	Left lower	1
	Clinical stage	IIIA
Radiotherapy sequence	IIIB	12
	CFRT before SBRT boost	3
PTV _{PT} volume (cc)	CFRT after SBRT boost	17
	Median (range)	30.7 (10.9–100.1)
PTV _{LN} volume (cc)	Median (range)	199.5 (24.8–452.3)
Min distance _(PT to LN) (cm)	Median (range)	4.0 (1.2–7.1)
Overlapping slices thickness _(PT and LN) (cm)	Median (range)	1.9 (–4.5–6.1)
Volume ratio _(LN to total lung)	Median (range)	0.07 (0.01–0.14)
Volume ratio _(LN to ipsilateral lung)	Median (range)	0.12 (0.02–0.30)
Min distance _(PT to ESO) (cm)	Median (range)	5.83 (0.89–10.47)
Volume ratio of overlapping structure _(ESO and LN) to ESO	Median (range)	0.32 (0.00–0.87)
Min distance _(PT to heart) (cm)	Median (range)	4.27 (1.11–7.58)
Volume ratio of overlapping structure _(heart and LN) to heart	Median (range)	0.02 (0.00–0.05)
Volume ratio of overlapping structure _(heart and LN) to PTV _{LN}	Median (range)	0.07 (0.01–0.24)

To make the presentation more concise, PT represented PTV_{PT}, LN represented PTV_{LN}, ESO represented esophagus, CFRT represented conventional fraction radiotherapy, and SBRT represented stereotactic body radiotherapy. The explanation of each anatomical geometric parameter could be referred to Fig. 1

were transferred to MIM imaging system (MIM Software, Cleveland, USA). Average intensity projection CT (AIP-CT) and maximum intensity projection CT (MIP-CT) were acquired from MIM and transferred to the Pinnacle 9.10 treatment system (Philips, Fitchburg, USA).

For PTV of primary tumor (PTV_{PT}) delineation, ITV was delineated on MIP-CT using lung window-level. MIP-CT was rigidly registered with the AIP-CT, and then ITV was copied to AIP-CT. ITV was expanded 5 mm uniformly to form PTV_{PT}. The diagnostic FDG PET/CT was registered with AIP-CT for LN delineation. CTV of lymph node (CTV_{LN}) was delineated on AIP-CT using mediastinal window-level, and expanded 5–10 mm to form PTV of lymph nodes (PTV_{LN}). Appropriate adjustment of PTV_{LN} margin was made according to the actual motion of the patient. All contours were checked by a second dedicated radiation oncologist. AIP-CT was used for two kinds of hybrid plans.

CFRT & SBRT boost plan (C&S plan)

All C&S hybrid plans were retrospectively completed by a senior physicist on first planning 4D-CT, including the three patients who received CFRT before SBRT boost.

C&S hybrid plans were made by CFRT and SBRT boost plans. CFRT dose regime for LN was 2 Gy × 30f, and SBRT dose regimes for PT were ranged from 7.5 Gy × 8f to 12.5 Gy × 4f. For fair comparison, 12.5 Gy × 4f of SBRT dose regime was used for all hybrid plans in this study. All hybrid plans were made in Pinnacle 9.10 treatment planning system, and the selected linac for hybrid plans delivery was EDGE Linac (Varian, Palo Alto, USA).

All CFRT plans were made by 5–8 step-and-shoot IMRT fields with 6MV-X for PTV_{LN}, and the planning method was presented in our previous work [13]. All plans were optimized by direct machine parameter optimize (DMPO) algorithm, and plan dose was calculated by Collapsed Cone Convolution Superposition (CCCs) algorithm built in planning system. The isocenter of the fields was located at the centroid of PTV_{LN}, and the directions of the fields were adjusted to reduce the delivery to PTV_{PT}. Dose volume histograms (DVHs) of total lung, spinal cord, heart and esophagus should be as low as possible to reserve space for the SBRT plans (Additional file 1), while 95% volume of PTV_{LN} was covered by the prescription dose.

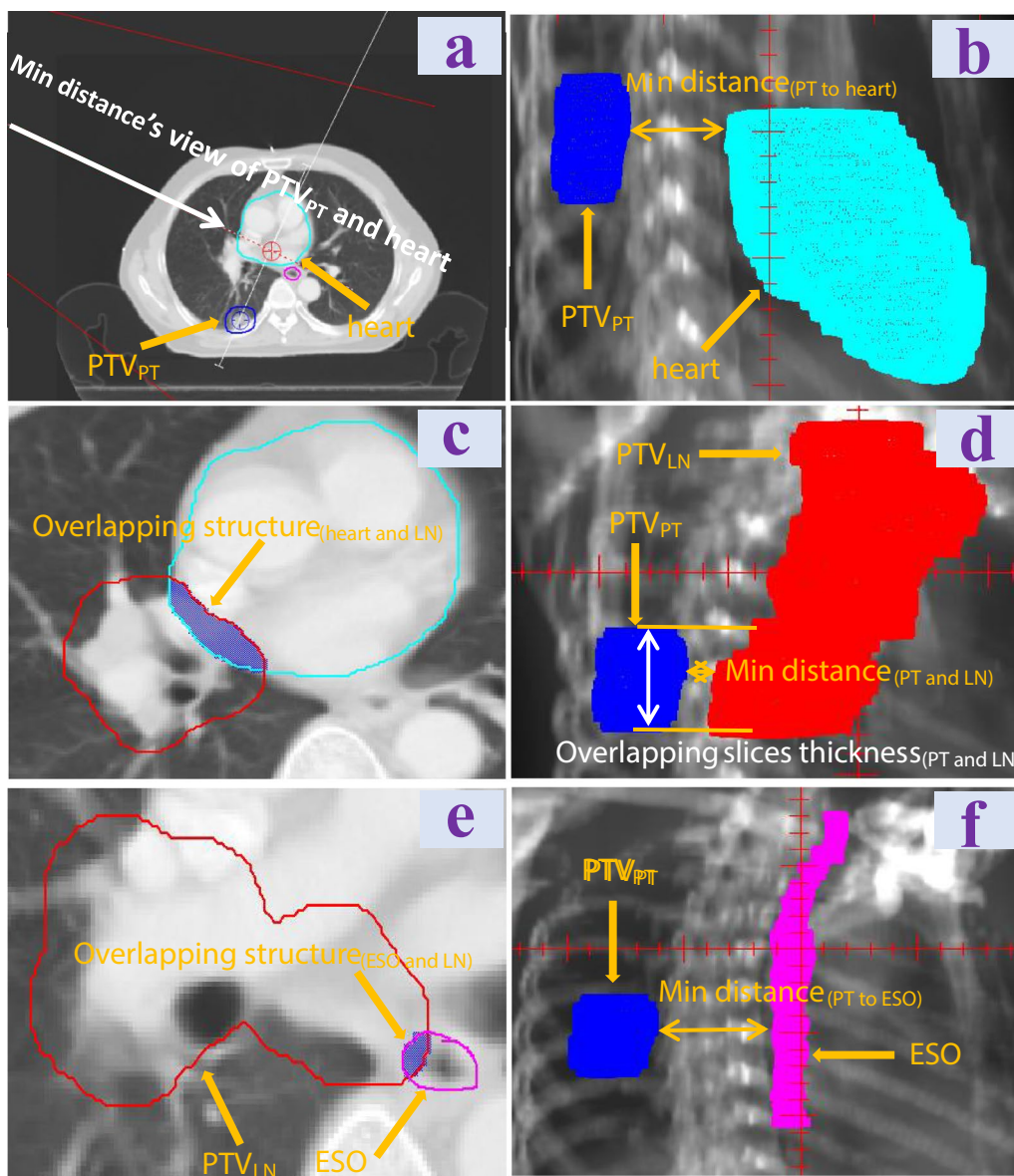


Fig. 1 Anatomical geometry features shown on CT images and min distance view's DRR images. **a** Min distance's view of PTV_{PT} and heart (the view direction is vertical to the centers' connection of PTV_{PT} and heart on CT slice); **b** Min distance_(PT to heart) shown on corresponding min distance view's DRR image; **c** Volume ratio of overlapping structure_(heart and LN) to heart or PTV_{LN}; **d** Min distance_(PT to LN) and overlapping slices thickness_(PT and LN) shown on corresponding min distance view's DRR image; **e** Volume ratio of overlapping structure_(ESO and LN) to ESO; and **f** Min distance_(PT to ESO) shown on corresponding min distance view's DRR image

SBRT boost plans were made by 9–11 coplanar IMRT fields for PTV_{PT}, and it's different from Haasbeek's 8–12 non-coplanar 3D-conformal beams [14]. Each SBRT beam was optimized to produce a single segment, and the minimum segment aperture allowed was 3.5 cm, which corresponded to the projection of each individual beam's-eye view of the PTV_{PT}. This method offered a coverage of primary tumor volume

in delivery and a steeper dose drop around PTV_{PT}. The isocenter of SBRT fields was located at the centroid of PTV_{PT}, and the directions of the fields were adjusted to reduce the delivery to PTV_{LN}. The dose drop from the boundary of PTV_{PT} to 50% isodose line of the prescription dose had better be within 6 mm for SBRT plans. Unintended dose (D₉₉) to PTV_{PT} obtained in CFRT plan was reduced from EQD₂ corrected prescription dose of PTV_{PT}, then the remaining EQD₂

dose was converted to actual fraction dose of SBRT in proportion. The OARs dose constraints of SBRT plans should allow for the remaining space from CFRT plans.

CFRT & SIB plan (C&SIB plan)

C&SIB hybrid plans were made from CFRT and sequential SIB plans, and the workflow of C&SIB was described

in Fig. 2. CFRT dose regime for LN was 2 Gy × 26f, and sequential 2 Gy × 4f for LN was combined with 12.5 Gy × 4f simultaneous integrated boost for PT. CFRT plans of C&SIB were consistent with those of C&S planning. Directions and isocenters of sequential SIB beams were consistent with those of CFRT and SBRT in C&S planning. Fixed-jaw method was used to limit the jaw

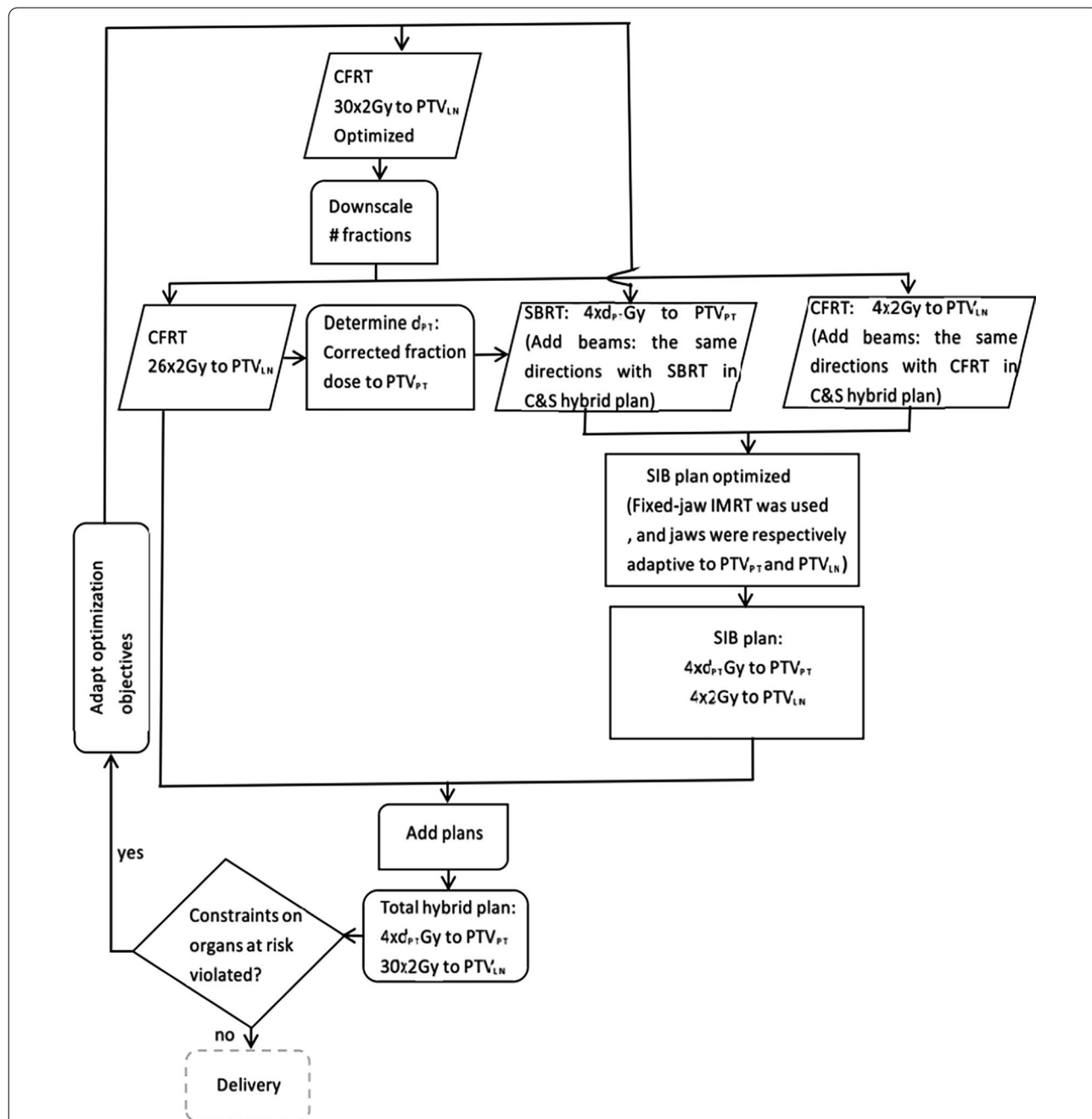


Fig. 2 Workflow of C&SIB hybrid plan. PTV_{LN}=Planning Target Volume (PTV) of lymph nodes, PTV_{PT}=PTV of primary tumor, d_{PT}=fraction dose to primary tumor of SIB plan

positions so that PTV_{PT} and PTV_{LN} could be covered by adaptive aperture of corresponding field. The method to calculate actual prescription dose of PTV_{PT} was the same with that of C&S planning, that allowed for intended dose obtained in 26 fractions of CFRT plans. The OARs dose constraints of SIB plans should allow for the remaining space from 26 fractions of CFRT plans (Additional file 1).

Plan parameters

Physical plan parameters were derived from two kinds of hybrid plans in Pinnacle 9.10 system. Planning CT, RT structure, RT plan and RT dose of SBRT and SIB plans of each patient were then respectively imported into Matlab R2016a (The MathWorks Inc., MA, USA). SBRT and SIB plan dose were corrected by voxel-wise EQD₂ [15] dose using an in-house Matlab script. EQD₂ corrected SBRT and SIB dose were respectively superposed with 30 and 26 fractions physical plan dose of CFRT to acquire EQD₂ plan parameters of C&S and C&SIB plans in Monaco planning system (Elekta, Stockholm, Sweden).

Physical plan parameters included: PTV_{LN} CI_{60Gy}; $PTV_{(PT+LN)}$ CI_{60Gy}; V_{20} and mean lung dose (MLD) of total lung and ipsilateral lung; spinal cord D_{max} ; heart D_5 , D_{30} , D_{max} and mean heart dose (MHD); esophagus D_{max} and V_{50} . EQD₂ plan parameters were the same with physical plan parameters except PTV_{PT} CI_{140Gy}. The Conformity Index (CI) formula is $CI = V_{RX}^2 / (TV \times V_{RI})$, where TV is the structure volume, V_{RX} is the structure volume covered by the Dose of Interest and V_{RI} is the total volume of the Dose of Interest. The Homogeneity Index (HI) formula is $HI = D_5 / D_{95}$, where D_5 is the dose covered 5% volume of the structure, and D_{95} is the dose covered 95% volume of the structure (Additional file 2).

Regression models

There were four works included in this work: (1). Regression models were established between physical plan parameters and anatomical geometry features listed in Table 1. (2). Spearman's correlation coefficients between physical and EQD₂ plan parameters were calculated to verify the possibilities of regression models of EQD₂ plan parameters. Models were also tried to establish between EQD₂ plan parameters and anatomical geometry features. (3). The consistence of coefficients of determination (R^2) of regression models between physical and EQD₂ plan parameters was determined. Its correlation to spearman's correlation coefficients (r) between physical and EQD₂ plan parameters for two kinds of hybrid plans was investigated. (4). Physical and EQD₂ plan parameters were respectively compared with models predictions to verify the effectiveness of the models by two new patients.

Data analysis

Regression models of plan parameters were established by SPSS 20 statistical software (IBM, USA). It showed high goodness of model fitting when R^2 (Coefficients of determination) ≥ 0.7 , moderate goodness of model fitting when $0.7 > R^2 \geq 0.5$, and poor goodness of model fitting when $R^2 < 0.5$. Spearman's correlation analysis between physical and EQD₂ plan parameters was also performed using SPSS 20 statistical software. Physical and EQD₂ parameters showed high correlations when $r \geq 0.8$; and moderate correlations when $0.8 > r \geq 0.6$.

Results

Regression models of physical plan parameters

For physical plan parameters, we established regression models between physical plan parameters and anatomical geometry features for two kinds of hybrid plans. PTV_{LN} CI_{60Gy} showed a high linear correlation with PTV_{PT} volume, PTV_{LN} volume, and min distance_(PT to LN) for both kinds of hybrid plans ($R^2 = 0.811$, $P < 0.001$ for C&S plans, and $R^2 = 0.779$, $P < 0.001$ for C&SIB plans).

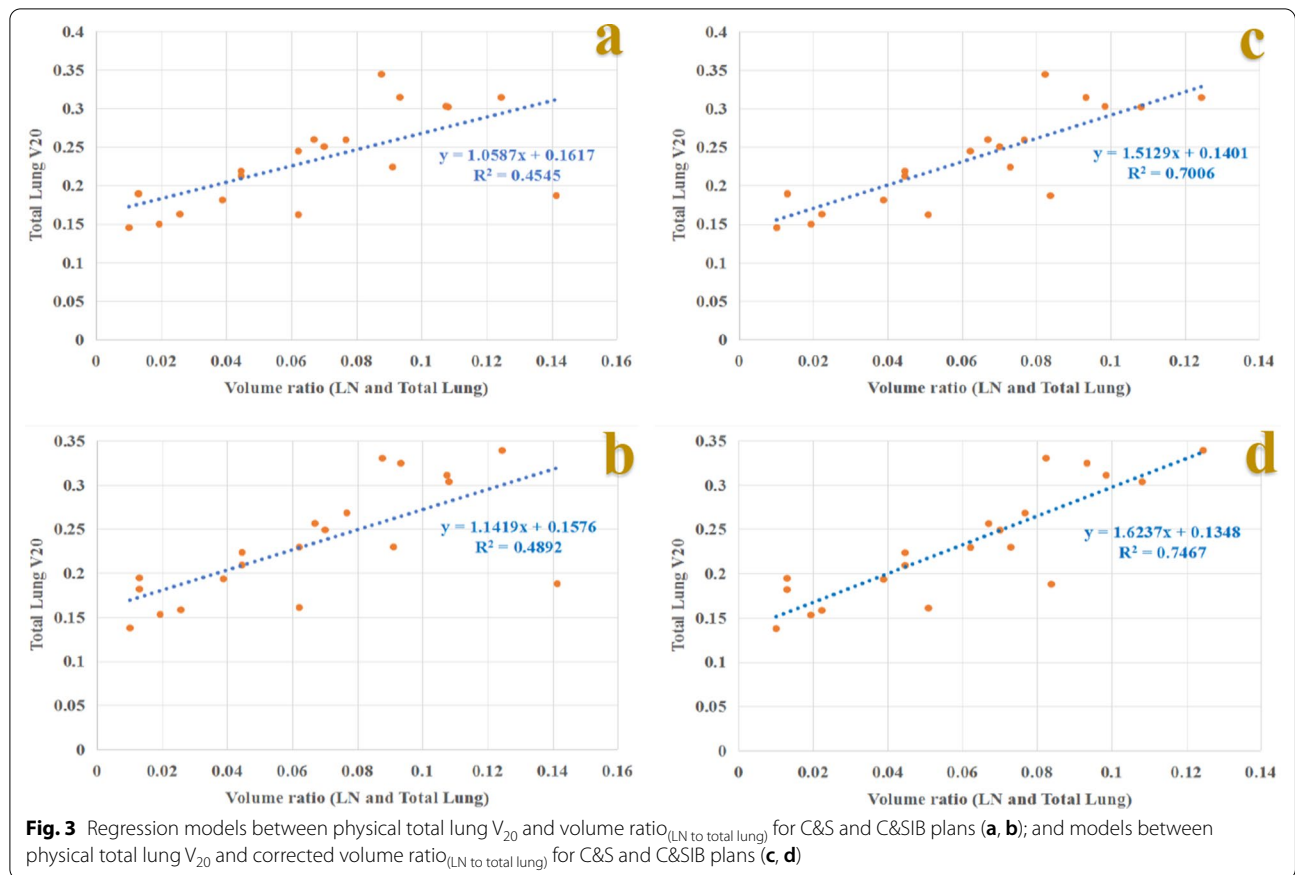
$PTV_{(PT+LN)}$ CI_{60Gy} showed a high linear correlation with PTV_{PT} volume, PTV_{LN} volume, min distance_(PT to LN), and overlapping slices thickness_(PT and LN) ($R^2 = 0.820$, $P < 0.001$ for C&S plans, and $R^2 = 0.833$, $P < 0.001$ for C&SIB plans).

V_{20} (Fig. 3a, b) and MLD of total lung showed poor linear correlations with volume ratio_(LN to total lung) ($R^2 = 0.455$, $P < 0.001$ and $R^2 = 0.450$, $P < 0.001$ for C&S plans; $R^2 = 0.489$, $P < 0.001$ and $R^2 = 0.487$, $P < 0.001$ for C&SIB plans). When neck lymph node metastasis was excluded from PTV_{LN} volume, V_{20} (Fig. 3c, d) and MLD of total lung showed high linear correlations with corrected volume ratio_(LN to total lung) ($R^2 = 0.701$, $P < 0.001$ and $R^2 = 0.703$, $P < 0.001$ for C&S plans; $R^2 = 0.747$, $P < 0.001$ and $R^2 = 0.730$, $P < 0.001$ for C&SIB plans).

V_{20} and MLD of ipsilateral lung showed moderate linear correlations with min distance_(PT to LN), volume ratio_(PT to ipsilateral lung), and corrected volume ratio_(LN to ipsilateral lung).

When heart was partially overlapped with PTV_{LN} , heart D_{30} and MHD showed high correlations of S type function with volume ratio of overlapping structure_(heart and LN) to PTV_{LN} (R_{HLL}) (Heart $D_{30} = e^{8.11-0.024/R_{HLL}}$, $R^2 = 0.767$, $P < 0.001$; MHD = $e^{7.677-0.017/R_{HLL}}$, $R^2 = 0.708$, $P < 0.001$ for C&S plans, and heart $D_{30} = e^{8.098-0.024/R_{HLL}}$, $R^2 = 0.775$, $P < 0.001$; MHD = $e^{7.656-0.017/R_{HLL}}$, $R^2 = 0.700$, $P < 0.001$ for C&SIB plans). Heart D_5 showed a moderate correlation of S function with volume ratio of overlapping structure_(heart and LN) to PTV_{LN} .

When esophagus was partially overlapped with PTV_{LN} , physical esophagus D_{max} showed a moderate inverse function with min distance_(PTVPT to ESO) for C&SIB plans



($R^2=0.692, P<0.001$). Esophagus V_{50} had a moderate correlation of cubic function with volume ratio of overlapping structure_(ESO and LN) to ESO ($R^2=0.648, P=0.005$ for C&S plans; and $R^2=0.695, P=0.002$ for C&SIB plans).

Regression models of EQD₂ plan parameters

Possibilities of regression models of EQD₂ plan parameters were investigated by the correlations between physical and EQD₂ plan parameters. Spearman’s correlation coefficients were calculated between physical and EQD₂ plan parameters, and the correlations were statistically significant for all plan parameters. Physical and EQD₂ parameters showed high correlations ($r \geq 0.8$) for $PTV_{LN} CI_{60Gy}$, total lung V_{20} and MLD, ipsilateral lung V_{20} and MLD, esophagus V_{50} and D_{max} , heart D_{30} and MHD (Fig. 4). Moderate correlations ($0.8 > r \geq 0.6$) were shown for $PTV_{(PT+LN)} CI_{60Gy}$, heart D_5 and D_{max} .

For EQD₂ plan parameters, regression models were also established for two kinds of hybrid plans. $PTV_{LN} CI_{60Gy}$ showed a high linear correlation with PTV_{PT} volume, PTV_{LN} volume, and min distance_(PT to LN) for

both kinds of hybrid plans ($R^2 = 0.85, P < 0.001$ for C&S plans, and $R^2 = 0.812, P < 0.001$ for C&SIB plans).

$PTV_{(PT+LN)} CI_{60Gy}$ showed a linear correlation with PTV_{PT} volume, PTV_{LN} volume, min distance_(PT to LN), and overlapping slices thickness_(PT and LN) ($R^2 = 0.845, P < 0.001$ for C&S plans, and $R^2 = 0.668, P = 0.002$ for C&SIB plans).

Total lung MLD showed a linear correlation with volume ratio_(LN to total lung) and volume ratio_(PT to total lung) (Fig. 5a, b) ($R^2 = 0.550, P = 0.001$ for C&S plans; $R^2 = 0.522, P = 0.002$ for C&SIB plans). When neck lymph node metastasis was excluded from PTV_{LN} volume, total lung MLD showed a high linear correlation with corrected volume ratio_(LN to total lung) and volume ratio_(PT to total lung) (Fig. 5c, d) ($R^2 = 0.756, P < 0.001$ for C&S plans; $R^2 = 0.766, P < 0.001$ for C&SIB plans).

Total lung V_{20} showed a linear correlation with corrected volume ratio_(LN to total lung) ($R^2 = 0.663, P < 0.001$ for C&S plans; $R^2 = 0.705, P < 0.001$ for C&SIB plans).

V_{20} and MLD of ipsilateral lung respectively showed moderate and high linear correlations with three geometry features of min distance_(PT to LN), volume ratio_(PT to ipsilateral lung), and corrected volume ratio_(LN to ipsilateral lung).

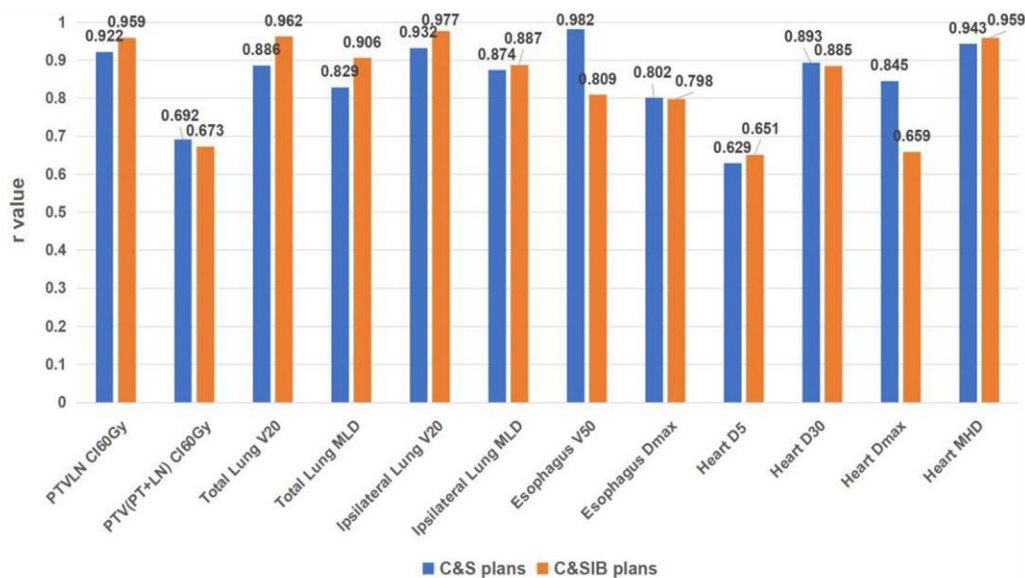


Fig. 4 Spearman's correlation coefficients between physical and EQD₂ plan parameters for two kinds of hybrid plans

When heart was partially overlapped with PTV_{LN}, heart D₅ showed a high correlation of S type function with volume ratio of overlapping structure_(heart and LN) to heart ($R^2 = 0.867$, $P < 0.001$ for C&S plans, and $R^2 = 0.842$, $P < 0.001$ for C&SIB plans). Heart D₃₀ had a moderate correlation of S type function with volume ratio of overlapping structure_(heart and LN) to PTV_{LN}, while MHD had a moderate correlation of S type function with volume ratio of overlapping structure_(heart and LN) to heart. Heart D_{max} showed a moderate correlation of inverse function with min distance_(PTVPT to heart) ($R^2 = 0.573$, $P = 0.031$ for C&S plans; and $R^2 = 0.621$, $P = 0.001$ for C&SIB plans).

Esophagus D_{max} had a moderate correlation of inverse function with min distance_(PTVPT to ESO).

Fitting goodness of regression models

Coefficients of determination (R^2) of regression models of physical and EQD₂ plan parameters for two kinds of hybrid plans were shown in Fig. 6.

For the parameters of PTV_{LN} CI_{60Gy}, total lung V₂₀ and MLD, ipsilateral lung MLD, heart D₅ and MHD, it indicated that the consistence of the fitting goodness of regression models between physical and EQD₂ plan parameters of C&SIB plans was better than that of C&S plans, while the correlations between physical and EQD₂ plan parameters of C&SIB plans were higher than those of C&S plans (Fig. 4).

For the parameters of PTV_(PT+LN) CI_{60Gy}, esophagus V₅₀, and heart D₅, the consistence of the fitting goodness of regression models between physical and EQD₂ plan

parameters of C&SIB plans was poorer than that of C&S plans, while the correlations of C&SIB plans were lower than those of C&S plans.

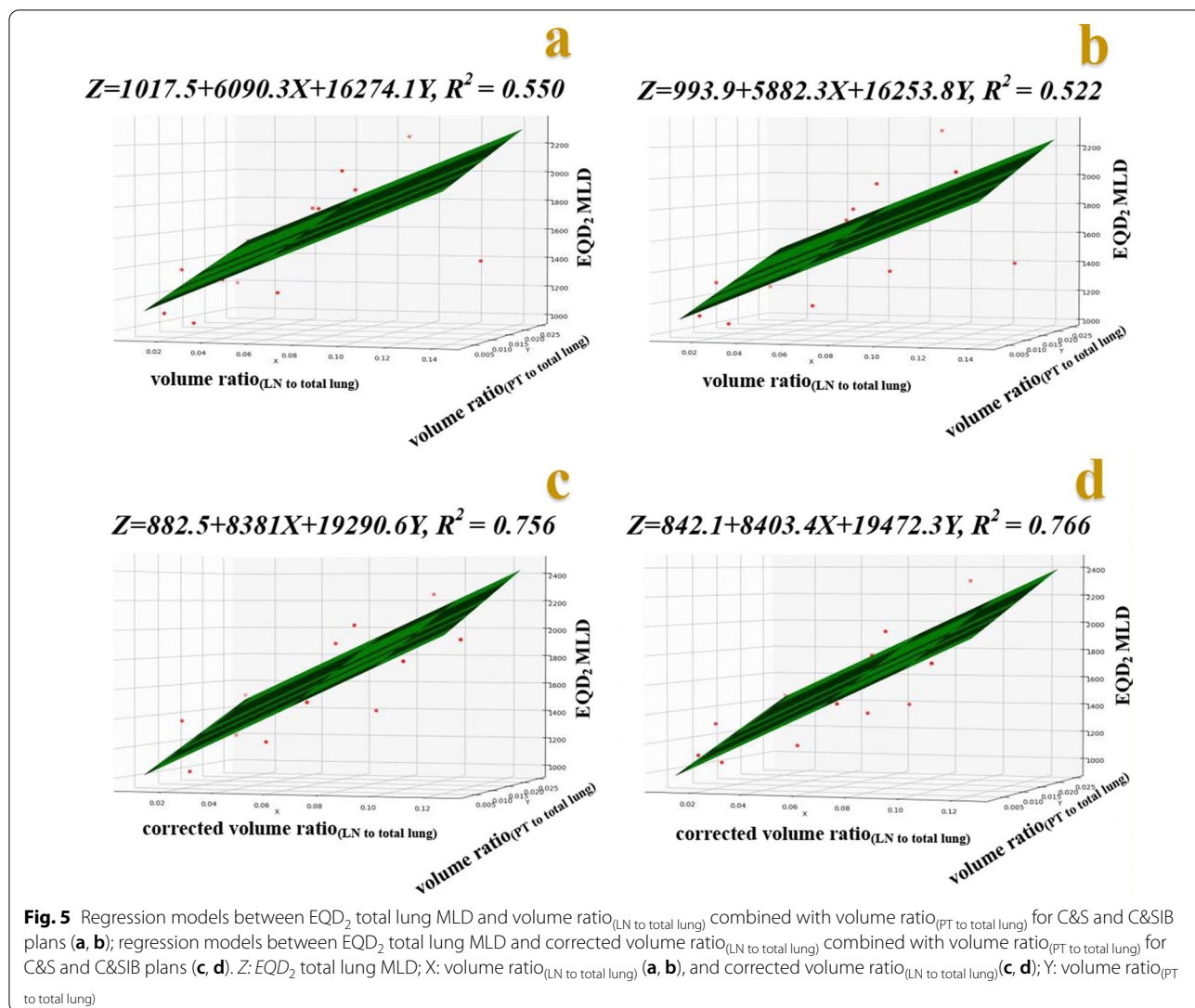
As the correlation between physical heart D_{max} and min distance_(PTVPT to heart) couldn't be established in this work, meanwhile, the correlation between physical esophagus D_{max} and min distance_(PTVPT to ESO) couldn't be established for C&S plans, we didn't show these results in Fig. 6.

Effectiveness of regression models

Figure 7 shows the performance of the models of physical and EQD₂ plan parameters for two kinds of hybrid plans.

It indicated that physical models predictions of PTV_{LN} CI_{60Gy}, total lung V₂₀, total lung MLD, and heart D₅ had good consistence with physical plan parameters for second patient (Fig. 7a, b). Meanwhile, for the physical plan parameters of total lung V₂₀, ipsilateral lung V₂₀, ipsilateral lung MLD, and esophagus V₅₀, physical models could predict that which kind of hybrid plan was high than the other one for two new patients.

EQD₂ models predictions of total lung V₂₀, total lung MLD, and heart D₃₀ had good consistence with EQD₂ plan parameters for the second patient (Fig. 7c, d). Meanwhile, for EQD₂ plan parameters of total lung V₂₀, ipsilateral lung V₂₀, and ipsilateral lung MLD, EQD₂ models could predict that which kind of hybrid plan was high than the other one for two new patients.



Discussion

For stage III NSCLC with solitary lung lesion and lymph node metastasis, regression models of physical and EQD₂ plan parameters were established based on anatomical geometry features for two kinds of hybrid plans in this study, and regression models had at least moderate fitting goodness. The possibilities of regression models of EQD₂ plan parameters were verified by the correlations between physical and EQD₂ plan parameters. The consistence of the fitting goodness of regression models between physical and EQD₂ plan parameters had a positive correlation with spearman’s correlation coefficients between physical and EQD₂ plan parameters for two kinds of hybrid plans. For physical and EQD₂ parameters of total lung V₂₀, ipsilateral lung V₂₀, and ipsilateral lung MLD, the models could predict that which kind of hybrid

plan was high than the other one for two new patients. PT of all hybrid plans were given a prescription dose of 4 × 12.5 Gy in this study.

At present, different strategies could be used for hybrid planning [7–12], and we chose two main methods in this work. C&S hybrid planning is simple and time-saving, but the interaction effect of hybrid plan components (CFRT and SBRT) is significant when the two lesions are close. C&SIB hybrid planning is complex and time-consuming. The first step of C&SIB planning (CFRT) to irradiate LN still has an impact on PT dose, although in the second step, the interaction effect could be reduced to a certain extent in the SIB plan optimization. Due to the different dose schemes of hybrid plan components (CFRT, SBRT and SIB), it would be more appropriate to convert the physical dose of the latter two plans to EQD₂ corrected dose in evaluation process of hybrid plans.

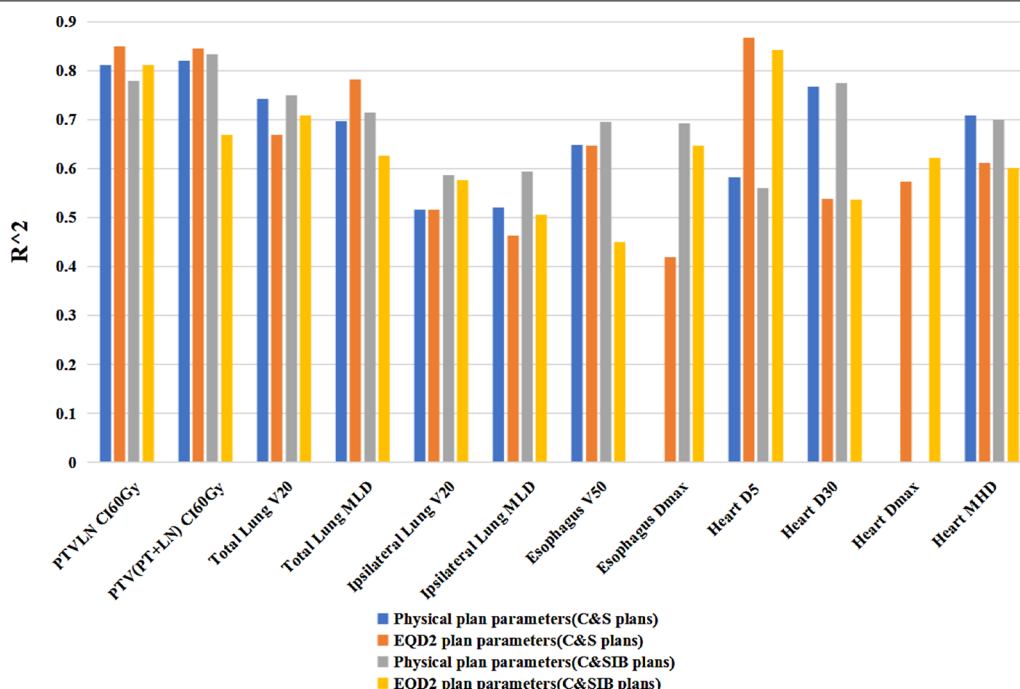


Fig.6 Coefficients of determination (R^2) for regression models between plan parameters listed in the X-axis and geometric parameters of the anatomy. Regression models were described by using the following format: *Plan parameter(geometric parameters of the anatomy): correlation type.* $PTV_{LN} CI_{60Gy}$ (PTV_{PT} volume, PTV_{LN} volume, and min distance_(PT to LN)): Linear correlation: $PTV_{(PT+LN)} CI_{60Gy}$ (PTV_{PT} volume, PTV_{LN} volume, min distance_(PT to LN), and overlapping slices thickness_(PT and LN)): Linear correlation. Total lung V_{20} (corrected volume ratio_(LN to total lung)): Linear correlation: Physical total lung MLD (corrected volume ratio_(LN to total lung)): Linear correlation: EQD₂ total lung MLD (corrected volume ratio_(LN to total lung) volume ratio_(PT to total lung)): Linear correlation: Ipsilateral lung V_{20} and MLD (min distance_(PT to LN) volume ratio_(PT to ipsilateral lung) and corrected volume ratio_(LN to ipsilateral lung)): Linear correlation: Heart D_{30} (volume ratio of overlapping structure_(heart and LN) to PTV_{LN}): S type function. Physical heart D_5 and MHD (volume ratio of overlapping structure_(heart and LN) to PTV_{LN}): S type function. EQD₂ heart D_5 and MHD (volume ratio of overlapping structure_(heart and LN) to Heart): S type function. EQD₂ heart D_{max} (min distance_(PTVPT to heart)): Inverse function. Physical esophagus D_{max} (min distance_(PTVPT to ESO)): Inverse function for C&SIB plans. EQD₂ esophagus D_{max} (min distance_(PTVPT to ESO)): Inverse function

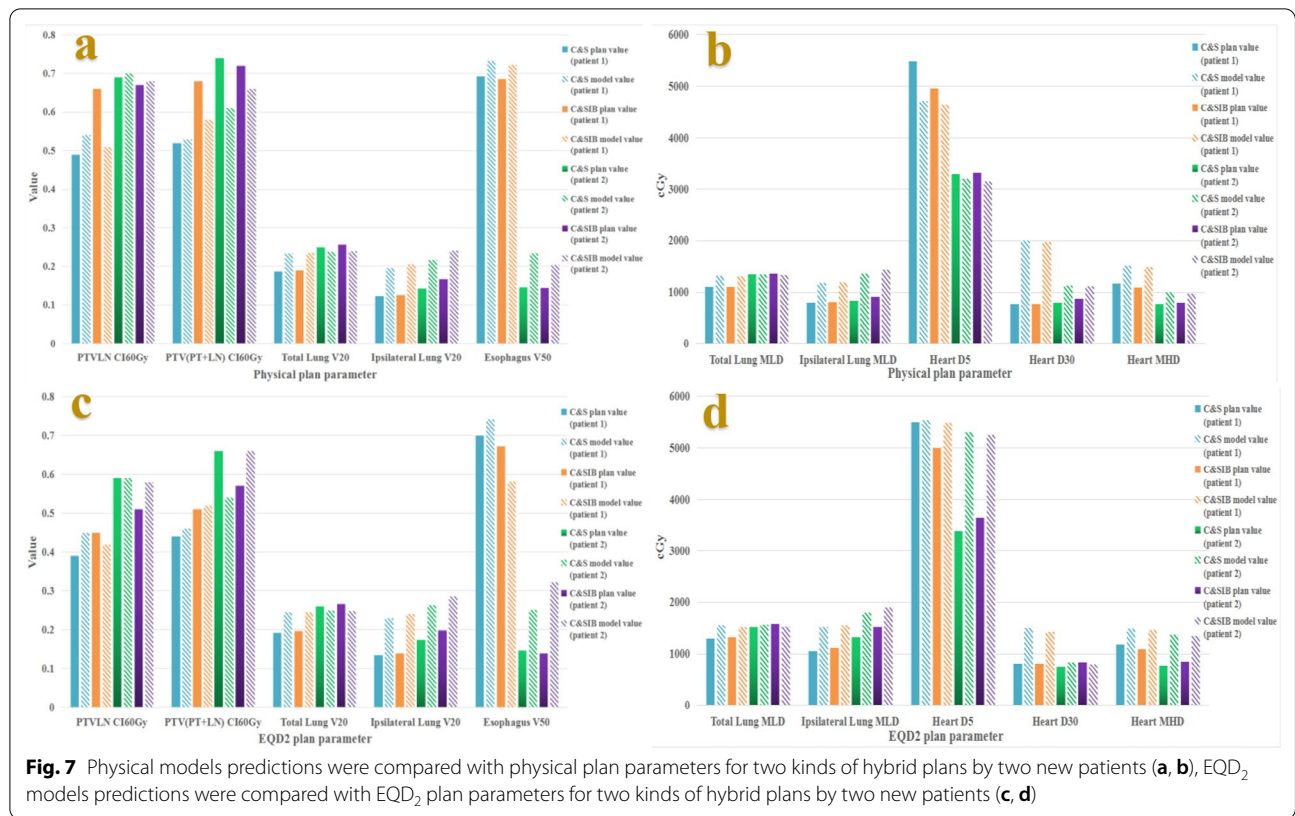
It's still not very clear which kind of hybrid planning has more dosimetric advantages, especially EQD₂ dose advantages when the patients have different anatomical geometry features. It would be indeterminate in choosing hybrid planning strategy under the above situation. Regression models of physical and EQD₂ plan parameters would be effective and time saving tools to solve such problems.

There have been few studies about the models for predicting physical plan parameters, especially EQD₂ plan parameters of two kinds of hybrid plans to our knowledge. The interaction effect of each kind of hybrid planning may be variously related to the geometry features, which provided us with inspiration and opportunity to find the optimal method of hybrid planning. This is the first research to assess the potential of regression models of physical and EQD₂ plan parameters for two methods of hybrid planning. Regression models of EQD₂ plan parameters proposed in this work were based on the assumption that we have used the appropriate EQD₂

calculation model for SBRT and SIB plans [15], and the correct target and OARs α/β values [16].

For the three patients who received CFRT before SBRT boost in this work, the generation of a summed up plan was even more difficult due to the presence of two planning CTs and different geometries of the anatomy and the tumor, hybrid plans were retrospectively made for these three patients the same as the other seventeen patients on the first planning 4D-CT. This would be suitable for the reason that the main purpose of this work is to propose the concept of plan parameters prediction models of two kinds of hybrid plans, while ignoring the changes of anatomical structure of the three patients during two planning CTs.

In this work, physical and EQD₂ plan parameters of $PTV_{LN} CI_{60Gy}$ have shown strong positive correlations with PTV_{LN} volume and min distance_(PT to LN), and strong negative correlations with PTV_{PT} volume for two kinds of hybrid plans. $PTV_{(PT+LN)} CI_{60Gy}$ is not only correlated with above three geometry features, but also negatively correlated with overlapping slices thickness_(PT and LN).



It could be inferred that interaction effect between two lesions is mainly affected by four features above.

PTV/lung volume ratio has been shown a reliable factor for predicting lung dose [17, 18]. In this study, as 6 out of 20 patients had neck lymph node metastasis, physical and EQD₂ total lung V₂₀ had poor linear correlations with volume ratio_(LN to total lung). It may be easy to understand that lung dose was almost unaffected by the volume of neck lymph node metastasis. When neck lymph node metastasis was excluded from PTV_{LN} volume, physical and EQD₂ total lung V₂₀ showed a high linear correlation with corrected volume ratio_(LN to total lung). Meanwhile, physical total lung MLD had a high linear correlation with corrected volume ratio_(LN to total lung), while EQD₂ total lung MLD was not only affected by corrected volume ratio_(LN to total lung) but also volume ratio_(PT to total lung). It can be explained that EQD₂ lung dose around PTV_{PT} was nearly 3.1 times than physical lung dose (EQD₂ dose = $D(d + \alpha/\beta)/(2 + \alpha/\beta)$, D: total dose (50 Gy); d: fraction dose (12.5 Gy); lung $\alpha/\beta = 3$) [15, 16], while PTV_{PT} volumes were much smaller than PTV_{LN} volumes. As a result, the presence of PTV_{PT} didn't significantly affect physical and EQD₂ total lung volume dose, such as V₂₀, but could affect EQD₂ total lung MLD.

It also revealed that heart D₅, D₃₀ and MHD would be more susceptible to overlapping structure_(heart and LN).

Another interesting result was that min distance_(PT to ESO) may be an important feature for predicting EQD₂ esophageal max dose for hybrid plans. It indicated that hybrid plans components (SBRT or SIB) may also have an important influence on EQD₂ esophageal max dose, though we may pay more attention on the influence of CFRT plans.

A similar knowledge-based planning solution called RapidPlan [19, 20] takes a library of precious treatment plans and uses regression analysis to determine correlations between geometric and dosimetric features of the planning target volumes (PTVs) and OARs of the library plans. This method forms the model, and the model is then used to predict a range of achievable plan parameters for a prospective patient. For stage III NSCLC patients, it's challenging to predict the plan parameters of hybrid plans when PT received SBRT with different dose regimens and LN received CFRT. Physical and EQD₂ plan parameters derived from regression models could be used as benchmarking protocols of hybrid planning in routine practice with the models improved.

Under the assumption that EQD₂ dose calculation model is reliable (it's not the scope of this work), we've made sure that there were connections between physical and EQD₂ plan parameters, and it's feasible to establish the regression models of EQD₂ plan parameters. We

could see that the regression models had at least moderate goodness in this work. Meanwhile, the consistence of the fitting goodness of regression models between physical and EQD₂ plan parameters had a positive correlation with spearman's correlation coefficients between physical and EQD₂ plan parameters for two kinds of hybrid plans.

One of the most important purposes of this study was to investigate if regression models could exactly predict which kind of hybrid plan was superior to the other one for physical and EQD₂ plan parameters. As the patients selection was really hard, and the quantity of patients suitable for radiotherapy with hybrid plan was limited in this work, we could use only two new patients data in the models validation process. And frankly, this is a proof of concept which may work or not in the end when all of the variabilities in patient anatomies and anatomy of the disease itself were considered. As a pilot study, we thought it would be acceptable to some extent even if a statistically significant validation hasn't been done. From the validation results of two patients, we could preliminarily evaluate the effectiveness of the regression models.

For total lung V₂₀, ipsilateral lung V₂₀, and ipsilateral lung MLD, the models could predict that C&SIB plans were higher than C&S plans for two new patients. In this work, physical and EQD₂ models were based on 20 patients data including 4 patients whose mediastinal lymph node and primary lesions were located in left and right lobes respectively. As two new patients by whom we verified the models were exactly such patients, we could see that only several physical and EQD₂ models predictions, such as total lung V₂₀ and MLD, had good consistence with plan parameters for the second patient. This situation indicated that more patients needed to be used in the models fitting.

There were still some limitations in this work. First, lung cancer patients suitable for hybrid planning were highly selected. Most patients with stage III NSCLC have large central lung lesions, only approximately 5–10% of patients are suitable for hybrid planning. This number would likely increase in case of SBRT dose regime with more fractions. Secondly, the relationship between geometric features and physical/EQD₂ plan parameters derived from the 20 patients wasn't sufficient to cover the complete connection. As the patients increase, smarter models could be developed to predict the performance of different hybrid planning for stage III NSCLC.

In conclusion, regression models of physical and EQD₂ plan parameters were established for two kinds of hybrid planning, and the regression models had at least moderate goodness. The possibilities of regression models of EQD₂ plan parameters were verified by the correlations

between physical and EQD₂ plan parameters, and the consistence of the fitting goodness of regression models between physical and EQD₂ plan parameters had a positive correlation with spearman's correlation coefficients between physical and EQD₂ plan parameters. The models have a potential to predict physical and EQD₂ plan parameters for two kinds of hybrid planning. The models could be gradually developed into an automatic optimization method for hybrid planning based on prior knowledge.

Abbreviations

EQD₂: Equivalent Dose in 2 Gy/f; NSCLC: None-small cell lung cancer; CFRT: Conventional fraction radiotherapy; SBRT: Stereotactic Body Radiation Therapy; SIB: Simultaneous integrated boost; C&S plan: CFRT&SBRT plan; C&SIB plan: CFRT&SIB plan; DRR: Digitally reconstructed radiograph; PT: Primary tumor; LN: Lymph node; PTV_{PT}: PTV of PT; PTV_{LN}: PTV of LN; ITV: Internal target volume; ESO: Esophagus; R_{HLL}: Volume ratio of overlapping structure_(heart and LN) to PTV_{LN}; R_{HLLH}: Volume ratio of overlapping structure_(heart and LN) to heart; MLD: Mean lung dose; MHD: Mean heart dose; CI: Conformity Index; HI: Homogeneity Index.

Supplementary Information

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Additional file 1. Plan objectives for two kinds of hybrid planning.

Additional file 2. Physical and EQD₂ plan parameters of two kinds of hybrid plans.

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Authors' contributions

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

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Availability of data materials

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

Declarations

Ethical approval and Consent to participate

The study is a retrospective study. When the study began, all selected patients signed informed consents 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.

Competing interests

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

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