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Clinical association between plan complexity and the local-recurrence-free-survival of non-small-cell lung cancer patients receiving stereotactic body radiation therapy

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The authors have no relevant conflicts of interest to disclose.

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Abstract

Purpose: To investigate the clinical impact of plan complexity on the local recurrence-free survival (LRFS) of non-small cell lung cancer (NSCLC) patients treated with stereotactic body radiation therapy (SBRT).

Methods: Data from 123 treatment plans for 113 NSCLC patients were analyzed. Plan-averaged beam modulation (PM), plan beam irregularity (PI), monitor unit/Gy (MU/Gy) and spherical disproportion (SD) were calculated. The γ passing rates (GPR) were measured using ArcCHECK 3D phantom with 2%/2mm criteria. High complexity (HC) and low complexity (LC) groups were statistically stratified based on the aforementioned metrics, using cutoffs determined by their significance in correlation with survival time, as calculated using the R-3.6.1 packages. Kaplan-Meier analysis, Cox regression, and Random Survival Forest (RSF) models were employed for the analysis of local recurrence-free survival (LRFS). Propensity-score-matched pairs were generated to minimize bias in the analysis.

Results: The median follow-up time for all patients was 25.5 months (interquartile range 13.4-41.2). The prognostic capacity of PM was suggested using RSF, based on Variable Importance and Minimal Depth methods. The 1-, 2-, and 3-year LRFS rates in the HC group were significantly lower than those in the LC group ($p=0.023$), when plan complexity was defined by PM. However, no significant difference was observed between the HC and LC groups when defined by other metrics ($p>0.05$). All γ passing rates exceeded 90.5%.

Conclusions: This study revealed a significant association between higher PM and worse LRFS in NSCLC patients treated with SBRT. This finding offers additional clinical evidence supporting the potential optimization of pre-treatment quality assurance protocols.

Keywords

NSCLC; SBRT; Local recurrence; Quality assurance; Plan complexity

Introduction

The implementation of Stereotactic Body Radiation Therapy (SBRT) for early-stage non-small-cell lung cancer (NSCLC) patients has improved the local tumor control rates and a reduced incidence of normal tissue complications when compared to conventional fractionated treatment[1]. Nevertheless, local recurrence still occurs in a range of 8.1% to 16.1% of NSCLC patients treated with SBRT as their primary therapy[2]. Furthermore, a recent study revealed that 56% of in-field recurrences happened within the central high-dose region[3]. Therefore, investigating potential biological[4] and dosimetric factors is of clinical importance to mitigate the risk of recurrence in the future.

The radiobiological effects of radiotherapy are predominantly influenced by the dose distribution in treatment plans. More complex plans can lead to increased disparities between the planned and actual delivered radiation doses[5]. To reduce dosimetric deviation, plan parameters that reflect complexity, such as the γ passing rate (GPR), are routinely monitored as part of pre-treatment quality assurance (QA) procedures, either through dosimetric simulation[5] or physics measurements using phantoms, detector arrays, or films[6]. GPR serves as an indicator of the consistency between the planned dose and the measured/simulated dose distribution[5].

In addition to GPR, other less used definitions of plan complexity include plan-averaged beam modulation (PM), plan beam irregularity (PI), and monitor unit/Gy (MU/Gy), etc. PM quantifies the extent to which a large open field is divided into multiple smaller segments. PI characterizes deviations in aperture shapes from a regular circle[7]. MU/Gy reflects the overall modulation level of the plan by the ratio of monitor units to the average dose of the target volume. According to the literature[8,9], tumor shape may also influence plan complexity, and spherical disproportion (SD) can be used to reflect the degree to which the tumor shape approaches a sphere. Higher values of PM, PI, MU/Gy and SD, or lower values of GPR, suggest increased beam complexity.

However, it's important to note that physics deviations do not necessarily induce clinical impact. Moreover, the clinical effectiveness and sensitivity of various plan parameters may differ. To bridge the gap between physics-based treatment plans and their clinical consequences, it is crucial to investigate the impact of dosimetric parameters in conjunction with patient outcomes. In the case of NSCLC patients undergoing SBRT, the relationship between plan complexity and local recurrence-free survival (LRFS) remains unclear. This retrospective cohort study aims to explore this clinical relevance, potentially providing complementary evidence to support informed decision-making. For instance, it may help in selecting more effective plan complexity parameters for pre-treatment quality assurance, ultimately improving the clinical outcomes of NSCLC patients treated with SBRT.

Methods and patients

1.1 Physics plan parameters

The ArcCHECK (Sun Nuclear™) 3D phantom was employed to measure the 3D GPR for each plan using 2 mm/2% criteria[10]. PM, PI, MU/Gy and SD were calculated using Python 3.7, based on equations (1-2), equations (3-5), equation(6) and equation(7), respectively[7].

$$\mathrm{BM}_i = 1 - \frac{\sum_j(\mathrm{MU}_{ij} * \mathrm{AA}_{ij})}{\mathrm{MU}_i * \mathrm{U}(\mathrm{AA}_{ij})} \quad (1)$$

$$\mathrm{PM} = \frac{\sum_i(\mathrm{BM}_i * \mathrm{MU}_i)}{\mathrm{MU}_p} \quad (2)$$

$$\mathrm{AI}_{ij} = \frac{\mathrm{AP}_{ij}^2}{4\pi * \mathrm{AA}_{ij}} \quad (3)$$

$$\mathrm{BI}_i = \frac{\sum_j(\mathrm{MU}_{ij} * \mathrm{AI}_{ij})}{\mathrm{MU}_i} \quad (4)$$

$$\mathrm{PI} = \frac{\sum_i(\mathrm{BI}_i * \mathrm{MU}_i)}{\mathrm{MU}_p} \quad (5)$$

$$\mathrm{MU/Gy} = \frac{\mathrm{MU}_p}{\mathrm{D}_{\mathrm{PTV}}} \quad (6)$$

$$\mathrm{SD} = \frac{A_{\mathrm{GTV}}}{\sqrt[3]{36\pi V_{\mathrm{GTV}}^2}} \quad (7)$$

where MU_{ij} is the monitor units (MU) of control point *j* in beam *i*; AA_{ij} is the area of all MLC openings at each control point; $\mathrm{U}(\mathrm{AA}_{ij})$ is the union area of all apertures of

beam *i*; AP is the perimeter of MLC aperture. D_{PTV} is PTV mean dose; A_{GTV} and V_{GTV} are the surface area and volume of the gross tumor volume (GTV), respectively.

1.2 Acquisition of clinical data

This single-institution retrospective cohort study was approved by ethics committee (IRB#2020KT155) and was exempted from the requirement for informed consent. A total of 123 treatment plans from 113 NSCLC patients were examined. These patients underwent SBRT treatment according to consistent protocols at our hospital between April 2012 and May 2021. For the 9 patients with multiple targets, separate treatment plans were created for each target due to their relatively large separation. Plan complexity was assessed for each individual plan. The inclusion criteria were as follows: 1) patients with pathologically confirmed NSCLC, or diagnosed as primary NSCLC by multidisciplinary board; 2) patients with stage I-II NSCLC who received no previous local treatments; 3) patients with a lung metastasis smaller than 5 cm and a low burden as well as a good Eastern Cooperative Oncology Group performance status (ECOG-PS)[11–14].

1.3 Motion management and treatment planning

All patients were immobilized in supine position using personalized thermoplastic masks (F481B, Guangzhou Renfu Medical Equipment, China). Abdominal compression was applied to reduce respiratory motion for all patients. The GTV was contoured as the macroscopic tumor identified on the planning CT. The internal target volume (ITV) was extended from GTV by incorporating the margins evaluated on dynamic images. Planning target volume (PTV) was created by an isotropic expansion of 5 mm from ITV, compatible with the setup accuracy guided by fractional cone beam CT images and double confirmation by oncologists and physicists. Organs at risk (OARs) were delineated for dose optimization, including the trachea, great vessels, spinal cord, esophagus, heart, lungs, ribs and brachial plexus[15,16] etc.

As shown in table 1, various PTV prescription dose and fractionation schedules were used in this study, based on a personalized evaluation of the target size, location, and patients' ECOG-PS. Volumetric modulated arc therapy (VMAT) techniques were used

to optimize all treatment plans within the Varian Eclipse treatment planning system, utilizing 6MV or 10MV flattening-filter-free (FFF) photon beams from Varian TrueBeam systems. Density and heterogeneity corrections were applied during the treatment planning stage. All plans aimed to cover at least 95% of PTV with prescription dose. Dose constraints for organs at risk (OARs) were established in accordance with recommendations from RTOG 0915[17], RTOG 0813[16] and EORTC 221133[18] etc.

Table 1 Clinical characteristics of the cohort

Group	Total: 123 plans
Age, Median (Q1-Q3)	69 (63-77)
Gender, n (%)	
Male	71 (57.7%)
Female	52 (42.3%)
Pathology, n (%)	
SCC	21 (17.1%)
AD	85 (69.1%)
NSCLC, NOS	11 (8.9%)
Others[a]	6 (4.9%)
Stage, n (%)	
I	104 (84.6%)
II	4 (3.3%)
IV	15 (12.2%)
Treatment duration (days), Median (Q1-Q3)	10 (7-11)
PTV prescription/fractions (f), n (%)	
48Gy-55Gy/4f	20 (16.3%)
50Gy-60Gy/5f	33 (26.8%)
60Gy-64Gy/8f	68 (55.3%)
Others[b]	2 (1.6%)
PTV mean dose (Gy), Median (Q1-Q3)	60.9 (55.3-64.9)
PTV volume (cm^3), Median (Q1-Q3)	32.3 (20.4-48)
BED10, Median (Q1-Q3)	117.1 (112.4-120.8)
Tumor's location, n (%)	
Central	12 (9.8%)
Peripheral	111 (90.2%)
CCT, n (%)	
Yes	21 (17.1%)
No	102 (82.9%)
PM, Median (Q1-Q3)	0.44 (0.39-0.52)
PI, Median (Q1-Q3)	107.3 (62-167)
LRFS (months), Median (Q1-Q3)	24.2 (13.2-39.8)
Local Recurrence, n (%)	
Yes	15 (12.2%)
No	108 (87.8%)
γ passing rate (%)[c], Median (Q1-Q3)	96.9 (95.5-97.9)
MU/Gy, Median(Q1-Q3)	31.50(25.70-43.00)
SD, Median(Q1-Q3)	1.279(1.227-1.331)

1. a, including: adenosquamous carcinoma, large cell carcinoma, invasive mucinous adenocarcinoma and carcinoid tumor.

2. b, including: one plan had prescribed dose of 56Gy/7fx, one plan had prescribed dose of 60Gy/9fx.

3. c, γ passing rates (GPR) were measured using ArcCHECK 3D phantom with 2%/2mm criteria.

4. Abbreviations: Q1-Q3=first quartile to third quartile; SCC=Squamous cell carcinoma; AD=Adenocarcinoma; NSCLC, NOS=Non-small cell lung cancer, not otherwise specified; BED10=Biologically effective dose when $\alpha/\beta = 10$; CCT=Whether concurrent chemotherapy or targeted therapy was used; PM=Plan averaged beam modulation; PI=Plan averaged beam irregularity; LRFS=Local recurrence-free survival; SD= Spherical disproportion.

1.4 Propensity score matching

To mitigate bias in this retrospective study, we conducted propensity score matching (PSM) using the MatchIt package[19], ensuring balance in patient baseline covariates, as detailed in Table 2. The nearest neighbor matching method was used to create the synthetic populations with matched baseline covariates. Propensity scores were calculated through a logistic regression model that considered the following variables: age, gender, pathology, stage, BED10 (biologically effective dose calculated using the linear quadratic equation, assuming $\alpha/\beta = 10$)[20], tumor's location (central or peripheral), treatment durations between the first and last treatment days, volume of PTV, and the use of concurrent chemotherapy or targeted therapy (CCT). The variables used for PSM included those not directly related to plan complexity but potentially affecting LRFS[21,22]. These variable selections were aligned with previous relevant researches[23–28].

Table 2 clinical characteristics of the propensity-score matched PM cohort

Group	HC (n=47)	LC (n=47)	
Age, Median (Q1-Q3)	68 (63-78)	71 (64-78)	p=0.64
Gender, n (%)			p=1.00
Male	29 (61.7%)	28 (59.6%)	
Female	18 (38.3%)	19 (40.4%)	
Pathology, n (%)			p=0.53
SCC	6 (12.8%)	10 (21.3%)	
AD	38 (80.9%)	34 (72.3%)	
NSCLC, NOS	3 (6.4%)	3 (6.4%)	
Stage, n (%)			P=1.00
I	38 (80.9%)	39 (83.0%)	
II	2 (4.3%)	2 (4.3%)	
IV	7 (14.9%)	6 (12.8%)	
Treatment duration (days), Median (Q1-Q3)	10 (7-11)	10 (7-10)	p=0.78
PTV volume (cm^3), Median (Q1-Q3)	32.3 (19.6-52.7)	34.8 (20.1-47.0)	p=0.82
BED10, Median (Q1-Q3)	117.5 (113.0-120.3)	116.0 (112.7-119.8)	p=0.73
Tumor's location, n (%)			p=1.00
Central	6 (12.8%)	5 (10.6%)	
Peripheral	41 (87.2%)	42 (89.4%)	
CCT, n (%)			p=0.59
Yes	10 (21.3%)	7 (14.9%)	
No	37 (78.7%)	40 (85.1%)	
PM, Median (Q1-Q3)	0.51 (0.46-0.55)	0.37 (0.33-0.41)	P<0.001

Abbreviations: Q1-Q3 = first quartile to third quartile; HC = High complexity plan; LC = Low complexity plan; SCC = Squamous cell carcinoma; AD = Adenocarcinoma; NSCLC, NOS = Non-small cell lung cancer, not otherwise specified; BED10 = Biologically effective dose when $\alpha/\beta = 10$; CCT = Whether concurrent chemotherapy or targeted therapy was used; PM = Plan averaged beam modulation.

1.5 Follow-up protocols

Patients underwent a series of examinations throughout the treatment process to establish a reference baseline. These assessments occurred at the following intervals: before treatment initiation, weekly during treatment, 4-6 weeks after treatment completion, every 3 months for the first 2 years, and every 6 months for the subsequent 3 years. The examinations included chest and abdominal contrast-enhanced CT scans, cranial magnetic resonance imaging (MRI), and superficial

lymph node ultrasound. The evaluation of early and late treatment-related toxicities followed the guidelines outlined in the Common Terminology Criteria for Adverse Events, version 5.0.

Local failure was defined as the occurrence of recurrent or progressed lesions within the PTV region. Determination of failure was made through a meticulous comparison of cross-sectional diagnostic images with the treatment plans. To minimize potential misdiagnoses[29], patients exhibiting suspicious changes in CT scans underwent tissue biopsy, thoracic MRI, or positron emission tomography (PET) as necessary. Tumor markers were monitored at each follow-up, and a multidisciplinary board, comprising experienced thoracic radiation oncologists and radiologists, was convened when needed. In this study, patient outcomes were assessed in terms of LRFS, as it is the parameter most clinically relevant to the delivered dose distribution in patient tumors[30] and may be influenced by the aperture complexity of SBRT plans[7].

1.6 Statistical analysis

Fisher's exact test was performed for the categorical data. T-test was used for normally distributed continuous data, otherwise Wilcoxon test was performed. Shapiro-Wilk method was used for the normality test. Pearson correlation test was performed for the continuous data to assess the linear association between two variables, while Spearman rank correlation test was performed when at least one of the two variables was an ordinal categorical variable. Survival curves were determined using Kaplan-Meier method and were compared using Log-rank test. Cox regression and Random Survival Forest (RSF) models were used to estimate hazard ratio and 95% confidence intervals of each factor of interest. A two-sided p-value < 0.05 was considered as statistically significant.

To standardize for the varying absolute magnitudes of each factor, all numeric variables were subjected to Z-score normalization prior to PSM. We conducted one-to-one matching without replacement, utilizing a caliper width of 0.15, and the score-matched pairs were subsequently employed in our analyses.

The high complexity plan (HC) and low complexity plan (LC) groups were

statistically stratified according to complexity metrics respectively. Consistent with previous studies[31,32], the cutoff value was determined based on the significance of correlation with survival time. The application used the coxph function (survMisc package, R-3.6.1) from the survival package to fit a Cox proportional hazard model to the binary (local recurrence) and continuous covariates (local recurrence-free survival time). The cutpoint was then computed using the cutp function (survMisc package) to achieve a balance between sensitivity and specificity[31].

Compared to the Cox regression model, the advantage of the RSF model is that it does not require the satisfaction of proportional hazards assumptions and log-linear assumptions[33]. Additionally, RSF can be used to assess the importance of various variables in survival predictions. For instance, Variable Importance (VIMP) and Minimal Depth (MD) methods were used to evaluate the significance of each variable.

Results

The median follow-up time was 25.5 months for all patients (interquartile range 13.4-41.2). Local recurrence was observed in 15 targets out of 123 tumor sites (12.2%), which is comparable to the rates of 8.1% - 16.1% reported by other institutions[2]. The 3D GPR of all 123 plans was higher than 90.5% and met clinical requirements. Cohort PM, PI, MU/Gy, GPR and SD varied ranging from 0.27 to 0.80, 14.41 to 470.13, 18.07 to 63.07, 90.5% to 99.8% and 1.101 to 1.993, respectively. More details can be found in Table 1. Fig. 1 displays the correlation coefficients between different variables.

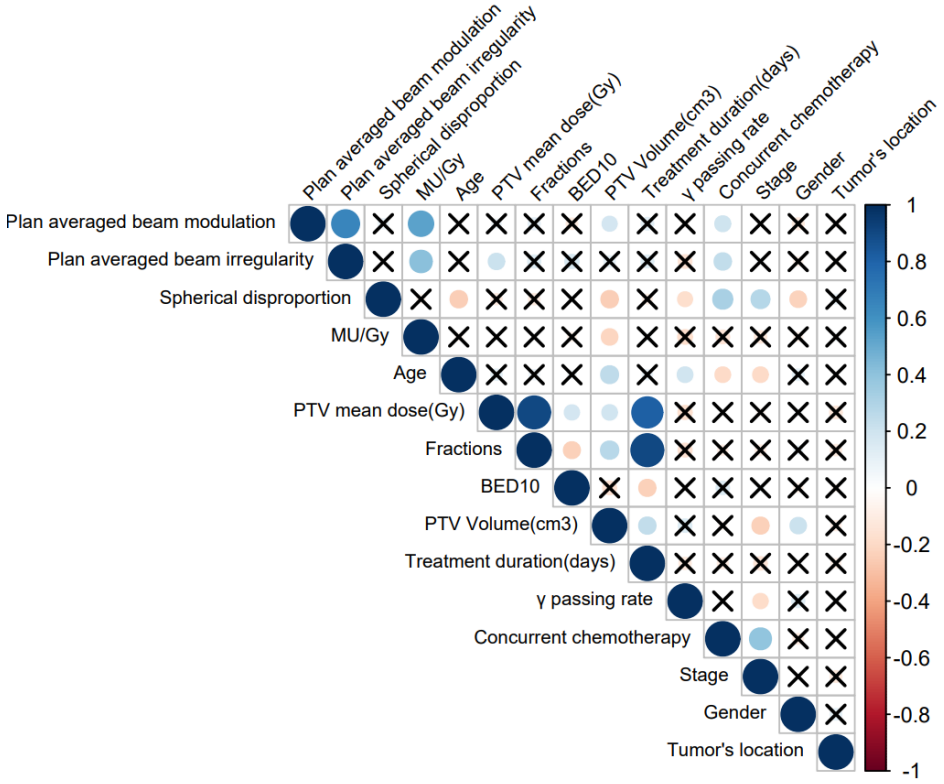

Figure 1. A heatmap showing the Pearson correlation coefficient or Spearman correlation coefficient between different variables. The X marked insignificant values according to the significant level: two-sided p-value < 0.05.

As shown in Table 2, PSM generated 47 data pairs using a cutoff value of 0.43 for PM. The Standard Mean Difference for PSM pairs based on logistic regression was 0.087 (<0.1), indicating a good match between the two groups. No significant differences in the variables between the two groups were observed.

As shown in Fig. 2, PM is an important variable in RSF model-based LRFS prediction, as confirmed by both VIMP (a) and MD (b) methods. When using a multivariable Cox regression model, a violation of the proportional hazards assumption was observed. As depicted in Fig. 3, the 1-, 2-, and 3-year LRFS rates of patients in the HC group were significantly lower than the corresponding rates of the LC group (Log-rank test: p = 0.023) when plan complexity was defined by PM using a cutoff value of 0.43. Considering other metrics were not significant in RFS analyses, the corresponding survival analysis results were not provided hereafter.

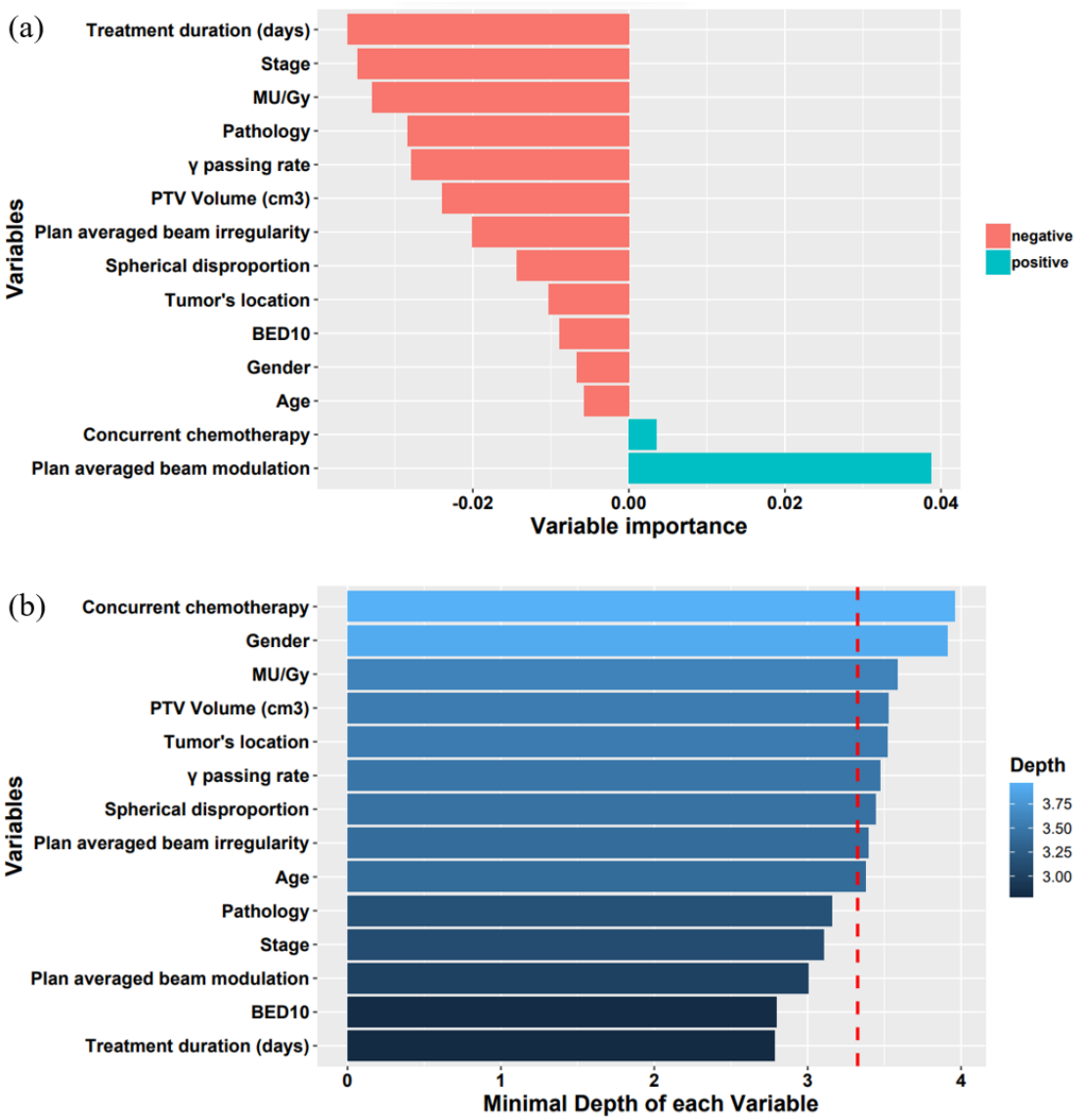

Figure 2. (a) Random Forest Variable Importance (VIMP). The blue and red bars indicate positive and negative VIMP respectively. Positive VIMP means that the variable improves the accuracy of prediction, proportional to the length of bars. (b) Minimal Depth (MD) variable selection. Low MD indicates important variables. The vertical dashed line is the threshold of maximum value for variable selection, which uses the mean of the MD distribution. Variables with MD lower than this threshold are important in forest prediction.

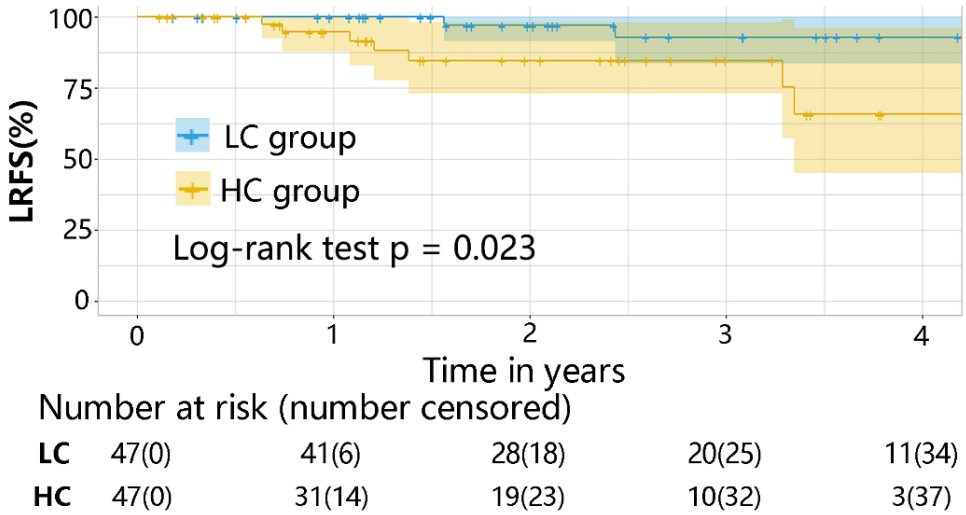

Figure 3. Kaplan-Meier plots of local recurrence-free survival for all patients. The plan complexity was determined by PM: plan averaged beam modulation. The shading areas indicate the 95% confidence intervals for the survival curves. The vertical tick marks on the curves indicate censored patients. Abbreviations: HC=High complexity; LC=Low complexity; LRFS=Local recurrence-free survival.

Discussion

Previous studies reported high local control rates after SBRT, ranging from 88.0% to 97.5% at 2- to 5-years[1,2,34], involving various RT regimen and BED10. Several hypotheses have been proposed to explain local recurrences after SBRT, including radiobiological and physical considerations. Radioresistant clonogens within the primary tumor site was a possible explanation to the inconsistent results of improving local control through dose-escalating and increasing BED10[4]. The underlying mechanisms of such resistance may include the proliferation of tumor stem cells during irradiation, the inherent insensitivity result from microenvironment alterations, the hypoxia status in target volume and etc[35]. However, unlike the radiobiological reasons, physical or technical explanations have been less investigated especially on the basis of clinical data. Recently, Nantavithya analyzed the pattern of local recurrence after SBRT by incorporating dosimetric parameters and geometric information, suggesting that some in-field recurrences might be ascribable to inadequate clearance of tumor clonogens due to underdose[3]. The LRFS of 90.5% at 2-year and 87.2% at 3-year observed in our study was comparable to previous reports of other centers, where 3-year LRFS ranged from 83.9% to 91.7%[36,37]. Based on these

clinical data, the impact of physics plan parameters on the local failure after SBRT was investigated retrospectively.

Compared with conventional radiotherapy, SBRT delivers much higher fractional conformal dose to the target[38], hence more severe consequences such as recurrence or OAR injury could happen if the high gradient dose missed the target. Respiratory motion, small field, and high dose rate using FFF beams have made it more challenging to perform SBRT for patients with lung cancer. Based on conventional fractionated plans, theoretical simulation[39] and dosimetric measurement[40] have been performed to evaluate the accuracy of dose delivery associated with plan complexity. This work provided additive and complementary clinical evidence that was missing in literature especially for NSCLC patients treated with SBRT, demonstrating significant association between high local recurrence and plan averaged beam modulation (PM) that can be used to guide clinical decision making in the future practice.

The observed significant correlation between higher PM and lower LRFS may be ascribable to the following physical explanations: 1) The combination of small target volume of SBRT cases and smaller beam segmentations in high PM plans increased their misalignment possibility[41], inducing larger deviations from the treatment plans than that of low PM cases; 2) It is more challenging for the smaller beam apertures in the high PM plans to follow the mobile target due to respiration, compromises the concordance between planned and delivered doses. Although fractionation may partially wash out the interplay effect, the less fraction number in SBRT reduced this opportunity[41–43]; 3) Over modulation may reveal the limitations in the beam models used in treatment planning systems; 4) SBRT delivers much higher fractional dose than conventional treatment, hence Flattening-Filter-Free (FFF) beams of higher dose rates (1400 MU/min or 2400 MU/min) are often used to improve the clinical efficiency, which also amplify the error of dose delivery associated with geometric discrepancy per time unit[44]. These factors may collectively undermine the robustness of delivered dose against motion for lung SBRT patients in a comprehensive way, and consequently reduced the LRFS.

As a broadly used metric for patient specific quality assurance, all measured GPR

values were larger than 90.5% and met clinical requirement. However, GPR was not associated significantly with patient clinical outcomes. As a possible explanation, rigid phantom-based GPR measurements was less sensitive to the plan complexity compared with less repeatable patient anatomies. Our observation of GPR was consistent with many previous studies[45-47], suggesting pre-treatment GPR cannot adequately reflect the complex clinical situations. In addition, the results of GPR are dependent on the different measurement approaches and algorithms[48,49], which reduces its quantitative consistency. To the contrary, the computation of PM is unique for a specific plan, making it more generalizable cross institutions.

Statistically, this study used PSM to ensure that exposed and unexposed subjects have similar distributions in the confounders, so as to better study the causal effect of exposure[50]. This method is different from multivariable models, which relied more heavily on correctly specified model. The multivariable analysis was not carried out because a violation of the proportional hazards assumption was identified when applying the multivariable Cox regression model. The Cox model presupposes that the hazard ratio between two individuals remains constant over time. If this assumption is violated, the model may yield inaccurate estimates of the hazard ratios, potentially leading to misleading interpretations of the covariates' effects on survival times. Therefore, consistent with previous relevant researches[51,52], PSM and RSF models were used in this study.

As for limitations, this retrospective study was based on a relatively small dataset. A prospective and randomized trial based on larger patient volume is desirable in the future to reconfirm the clinical value of PM for pretreatment QA.

Conclusions

Based on the long-term outcomes of NSCLC patients treated with SBRT, this study has contributed clinical evidence indicating that a higher degree of local recurrence is significantly correlated with higher plan-averaged beam modulation (PM). As a result, it suggests that plan complexity should be managed on a patient-specific basis in the future practice of lung SBRT.

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