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ORIGINAL ARTICLE

Estimation of the effect of target and normal tissue sparing based on equivalent uniform dose-based optimization in hypofractionated radiotherapy for lung cancer*

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Abstract

Objective This study aims to investigate the dosimetric differences among four planning methods of physical and biological optimization in hypofractionated radiation therapy for non-small cell lung cancer (NSCLC).

Methods Ten NSCLC patients receiving radiation therapy were chosen for this retrospective study. Volumetric modulated arc treatment plans for each patient were remade with dose-volume (DV) functions, biological-physical functions, and biological functions, using the same constraint parameters during optimization. The dosimetric differences between the four types of plans were calculated and analyzed.

Results For the target, equivalent uniform dose (EUD) of the EUD and EUD + DV groups was approximately 2.8%–3.6% and 3.2%–3.7% higher than those of the DV and DV + EUD groups, respectively. The average tumor control probability (TCP) of the EUD and EUD + DV groups was also significantly higher than those of the other two groups ($P < 0.05$). The difference in heterogeneity index (*HI*) among the four groups was also statistically significant ($P < 0.05$), while the difference of conformity index (*CI*) was not significant ($P > 0.05$). For the organs at risk, the differences of EUD, V_5, V_{10}, V_{20}, V_{30} of normal lung tissues were not statistically significant ($P > 0.05$); however, the mean lung dose of the EUD and EUD + DV groups was slightly lower than those of the other two groups.

Conclusion The biological optimization method has obvious advantages of improving EUD and TCP of the target, while decreasing the exposed dose of normal lung. This result is meaningful in choosing plan optimization methods in routine work.

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Key words: non-small cell lung cancer (NSCLC); equivalent uniform dose (EUD); hypofractionated radiotherapy; plan optimization

Currently, several commercial treatment planning systems (TPS) including Eclipse, Pinnacle, Monaco, and Raystation can perform accurate dose optimization and calculations in radiation therapy of various cancers. However, most of the TPSs only use the dose-volume (DV)-based physical functions when optimizing the inverse intensity modulated radiotherapy (IMRT) treatment plans. The main drawback of this optimization is that it does not represent the nonlinear response of the tumor and normal tissue to the irradiation. Furthermore, when calculating the dose, they all act on a certain point on the dose curve through the preset physical function [1], which has certain limitations and cannot regulate the overall dose distribution of the target or organs at risk (OAR). The biological function based on equivalent uniform dose (EUD), which involves the biological parameters of the interaction between irradiation and tissues, may compensate for the limitation of simple physical function

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optimization to some extent. This study intends to compare the results of different planning optimization methods based on physical function, physical function and biological function, and biological function, as well as the impacts of the different biological parameters on the target EUD and tumor control probability (TCP). The differences between the four different optimization methods in the stereotactic radiotherapy plan for lung cancer were evaluated to provide a dosimetric reference for clinical applications.

Materials and methods

Methods

EUD is a biological dose concept related to tissue biological characteristics proposed by Niemierko *et al*. It is defined as follows: for an anatomical structure exposed to nonuniform doses, the resulting radiobiological effects can be equivalent to a uniform dose distribution. This uniform dose is called EUD [2–3] for uneven dose distribution. EUD is a concept linking physical dose with TCP and normal tissue complication probability (NTCP) [3]. The formula for the EUD model is as follows:

$$EUD = (\frac{1}{N}\sum_{i=1} D_i^a)^{\frac{1}{a}} \quad (1)$$

The formula applies to both tumor and normal tissues. Here, N is the number of voxels in the region of interest (ROI), D_i is the dose of the i voxel in the ROI, and a is a biological characteristic parameter describing the dose-volume effect of the tumor or normal tissue. It was found that when $a \to +\infty$, the EUD converged to the maximum dose Dmax in the ROI region. From a clinical point of view, when a is given a large value, the high dose point in the ROI can be reflected by the EUD. When $a \to -\infty$, the EUD converges to the minimum dose Dmin of the ROI region. When EUD is used to evaluate the absorbed dose in the target region, a negative a-value is given. The cold spot of the absorbed dose is clearly reflected by the EUD. Similarly, when $a \to 1$, EUD is equivalent to the arithmetic average dose, and when $a \to 0$, the EUD converges to the geometric mean of the entire calculated volume dose. For tumor tissues, a is usually taken as a negative value with a large absolute value; for serial OAR, a is usually taken as a positive value with a large absolute value, while for parallel OAR, a is usually taken as a positive value with a small absolute value [4–8]. In this experiment, in order to show the relationship between the value of a and the dose-response of the target and lung tissues, the value of a for the target was selected to be in the range of –100 to –10, with intervals of 10; for lung tissue, the value of a was selected to be in the range of 0.1 to 1.0, and the interval were 0.1.

The widely used TCP calculation formula is as follows:

$$TCP = \frac{1}{1+(\frac{TCD_{50}}{EUD})^{4\gamma_{50}}} \quad (2)$$

Here, TCD_{50} is the dose required for a tumor control rate of 50%, and γ_{50} is the slope of the S-shaped dose-response curve of tumor tissue. TCD_{50} and γ_{50} are obtained from published clinical data. In this study, five groups of TCD_{50} and γ_{50} values in the literature were selected [9]; the calculated TCP results for each group were compared and analyzed.

The NTCP model is based on the TCP model assuming that there is no volume effect between the voxels of normal tissues [10]. NTCP calculation formula is similar to TCP:

$$NTCP = \frac{1}{1+(\frac{TD_{50}}{EUD})^{4\gamma_{50}}} \quad (3)$$

In the formula, TD_{50} is the dose at which the probability of normal tissue complications reaches 50%, and γ_{50} is the slope of the S-shaped dose-response curve of normal tissue, which can be replaced by $\frac{1}{m\sqrt{2\pi}}$, where m is derived from the LKB model and parameters related to the slope of the dose-response curve were also obtained from reported clinical data [11].

Treatment plan design

The CT images of 10 patients with non-small cell lung cancer (NSCLC) who had undergone radiation therapy were selected. The volumetric arc intensity therapy (VMAT) plan was designed using the Monaco system (version 5.11, ElektaAB, Stockholm, Sweden). The Monaco system can provide constraints based on both physical and biological functions. Four groups of plans were designed for each case: physical function constrained group (DV group) for both target and OAR, physical function for target and biological function for OAR constrained group (DV + EUD group),biological function for target and physical function for OAR constrained group (EUD + DV group), and biological function constrained group (EUD group) for both target and OAR. The prescription dose was 60 Gy/10 f [12], and it was ensured that the prescribed dose could enclose at least 95% of the target volume. The beginning angle of the gantry was set to 180°; one partial arc was 200°, two arcs per plan; the control point number was set as 120; the minimum calculation grid was 0.2 cm; and the calculation uncertainty was set to 1%. When the four groups of plans were optimized, they were consistent in terms of calculation parameters, dose-volume constraints for target, and OAR.

Calculation and statistical analysis

The Matlab software (version 2015a, MathWorks, US) was used to calculate the following values based on the treatment plan: (1) target EUD for each group of plans, taking *a* in the range of –100 to –10 with an interval of 10; (2) target TCP for each group under different target TCD_{50}/γ_{50} combinations [9]; (3) NTCP of normal lung (lung-GTV) tissue, taking a in the range of 0.1–1.0 with an interval of 0.1. In addition, the homogeneity index (*HI*), conformity index (*CI*) of the target and the dose-volume parameters of the OAR were compared.

The calculation formula for the target *HI* was:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \times 100\% \quad (4)$$

$D_{2\%}$ represents the maximum dose in the target, $D_{98\%}$ represents the minimum dose in the target, and $D_{50\%}$ is the median dose in the target [13]; the calculation formula for the target *CI* was:

$$CI = \frac{V_{T,Pi}}{V_T} \times \frac{V_{T,Pi}}{V_{Pi}} \quad (5)$$

Where $V_{T,Pi}$ represents the target volume enclosed by the prescription dose, V_T represents the volume of the target, and V_{Pi} represents the volume enclosed by the prescription dose. Statistical analyses were conducted using SPSS 20.0 for one-way analysis of variance. When $P < 0.05$, the difference was considered statistically significant.

Results

Tumor target

Table 1 shows the results of the PTV in the four groups of plans, where V_{60} is the percentage of the volume of the PTV wrapped by the prescription dose. It was found that $D_{2\%}$ and $D_{50\%}$ were higher in the EUD group and EUD + DV group than in the DV group and the DV + EUD group ($P < 0.05$), while the V_{60} and $D_{98\%}$ showed no significant difference ($P > 0.05$). Because the EUD function has a more powerful effect on the cold spot dose when performing target dose calculation [3], the result was closely related to the optimization characteristics of the EUD function.

Table 2 shows the EUD values of the target areas for the four groups of plans obtained when a different *a*-value was selected. It could be found that the EUD values of the EUD group and the EUD + DV group were significantly higher than those of the DV group and the DV + EUD group by 2.8%–3.6% and 3.2%–3.7%, respectively ($P < 0.05$). As the value of *a* decreases, the mean EUD of the four groups of plans also tended to decrease slightly, which specifically reflected the relationship between the *a*-value and EUD. The target TCP results for the four groups of plans are listed in Tables 3a–3d. It was found that the difference among the groups was statistically significant ($P < 0.05$) when the target area TCP values under different TCD_{50}/γ_{50} combinations in the four optimization methods were compared, showing that the value of TCD_{50}/γ_{50} had a greater impact on TCP. The statistical analysis results of *HI* and *CI* in the four groups are listed in Table 4. Through comparison and analysis, *HI* and *CI* were better in the DV + EUD group, and the difference in *HI* between the four groups was statistically significant ($P < 0.05$), whereas the difference in *CI* was not ($P > 0.05$).

In addition, regardless of the value of *a* and TCD_{50}/γ_{50}, the average TCP values of the EUD and EUD + DV groups

Table 1 Comparison of PTV parameters in four groups of plans

	DV group	DV + EUD group	EUD group	EUD + DV group	*P* value
V_{60} (%)	97.75 ± 1.02	98.45 ± 1.40	98.21 ± 1.72	98.04 ± 1.79	0.770
$D_{2\%}$ (Gy)	63.64 ± 0.38	63.66 ± 0.33	64.84 ± 0.62	65.05 ± 0.13	0.000
$D_{98\%}$ (Gy)	59.98 ± 0.22	60.18 ± 0.35	60.28 ± 0.96	60.20 ± 0.86	0.781
$D_{50\%}$ (Gy)	61.88 ± 0.13	61.94 ± 0.18	63.94 ± 0.61	63.26 ± 0.29	0.000

Table 2 EUD calculations results for four plan optimization methods with different *a*-values

a value	DV group (Gy)	DV + EUD group (Gy)	EUD group (Gy)	EUD + DV group (Gy)	*P* value
–10	89.56 ± 0.549	89.69 ± 0.334	92.47 ± 1.431	92.85 ± 0.616	0.000
–20	89.40 ± 0.518	89.55 ± 0.329	92.30 ± 1.433	92.68 ± 0.658	0.000
–30	89.24 ± 0.492	89.42 ± 0.327	92.13 ± 1.434	92.50 ± 0.700	0.000
–40	89.08 ± 0.471	89.29 ± 0.327	91.97 ± 1.435	92.33 ± 0.740	0.000
–50	88.93 ± 0.455	89.16 ± 0.328	91.80 ± 1.435	92.16 ± 0.779	0.000
–60	88.77 ± 0.447	89.03 ± 0.331	91.64 ± 1.434	92.00 ± 0.817	0.000
–70	88.62 ± 0.446	88.91 ± 0.334	91.48 ± 1.434	91.84 ± 0.853	0.000
–80	88.47 ± 0.454	88.79 ± 0.339	91.33 ± 1.434	91.68 ± 0.888	0.000
–90	88.32 ± 0.471	88.67 ± 0.344	91.17 ± 1.435	91.53 ± 0.921	0.000
–100	88.18 ± 0.496	88.55 ± 0.349	91.03 ± 1.437	91.39 ± 0.952	0.000

Table 3a TCP comparison of DV group with different TCD_{50}/γ_{50} values

a value	TCD_{50}/γ_{50} = 36.50/0.72	TCD_{50}/γ_{50} = 54.92/2.04	TCD_{50}/γ_{50} = 51.87/2.17	TCD_{50}/γ_{50} = 51.97/1.81	TCD_{50}/γ_{50} = 49.12/1.25	*P* value
–10	92.988 ± 0.115	98.182 ± 0.089	99.133 ± 0.046	98.091 ± 0.083	95.269 ± 0.138	0.000
–20	92.955 ± 0.109	98.156 ± 0.086	99.120 ± 0.044	98.067 ± 0.080	95.229 ± 0.132	0.000
–30	92.921 ± 0.104	98.130 ± 0.082	99.106 ± 0.042	98.042 ± 0.076	95.189 ± 0.126	0.000
–40	92.888 ± 0.100	98.104 ± 0.080	99.093 ± 0.041	98.018 ± 0.074	95.149 ± 0.122	0.000
–50	92.855 ± 0.097	98.077 ± 0.078	99.079 ± 0.040	97.993 ± 0.072	95.108 ± 0.118	0.000
–60	92.822 ± 0.096	98.051 ± 0.078	99.065 ± 0.040	97.969 ± 0.072	95.068 ± 0.117	0.000
–70	92.789 ± 0.097	98.023 ± 0.079	99.052 ± 0.041	97.944 ± 0.073	95.028 ± 0.118	0.000
–80	92.756 ± 0.099	97.996 ± 0.082	99.037 ± 0.042	97.919 ± 0.075	94.987 ± 0.122	0.000
–90	92.723 ± 0.104	97.969 ± 0.086	99.023 ± 0.045	97.894 ± 0.079	94.947 ± 0.128	0.000
–100	92.690 ± 0.110	97.941 ± 0.093	99.009 ± 0.048	97.868 ± 0.086	94.906 ± 0.136	0.000

Table 3b TCP comparison of DV + EUD group with different TCD_{50}/γ_{50} values

a value	TCD_{50}/γ_{50} = 36.50/0.72	TCD_{50}/γ_{50} = 54.92/2.04	TCD_{50}/γ_{50} = 51.87/2.17	TCD_{50}/γ_{50} = 51.97/1.81	TCD_{50}/γ_{50} = 49.12/1.25	*P* value
–10	93.016 ± 0.070	98.204 ± 0.054	99.144 ± 0.028	98.111 ± 0.050	95.303 ± 0.084	0.000
–20	92.987 ± 0.069	98.183 ± 0.054	99.133 ± 0.028	98.091 ± 0.050	95.269 ± 0.083	0.000
–30	92.959 ± 0.069	98.161 ± 0.054	99.122 ± 0.028	98.071 ± 0.050	95.236 ± 0.083	0.000
–40	92.932 ± 0.069	98.139 ± 0.055	99.111 ± 0.028	98.051 ± 0.051	95.202 ± 0.083	0.000
–50	92.905 ± 0.070	98.118 ± 0.055	99.100 ± 0.028	98.031 ± 0.051	95.170 ± 0.085	0.000
–60	92.878 ± 0.071	98.096 ± 0.057	99.089 ± 0.029	98.011 ± 0.052	95.137 ± 0.086	0.000
–70	92.851 ± 0.072	98.075 ± 0.058	99.078 ± 0.030	97.991 ± 0.053	95.104 ± 0.087	0.000
–80	92.825 ± 0.073	98.053 ± 0.059	99.067 ± 0.031	97.971 ± 0.055	95.072 ± 0.089	0.000
–90	92.798 ± 0.074	98.032 ± 0.062	99.056 ± 0.031	97.951 ± 0.056	95.040 ± 0.091	0.000
–100	92.772 ± 0.076	98.010 ± 0.062	99.045 ± 0.032	97.932 ± 0.057	95.008 ± 0.093	0.000

Table 3c TCP comparison of EUD group with different TCD_{50}/γ_{50} values

a value	TCD_{50}/γ_{50} = 36.50/0.72	TCD_{50}/γ_{50} = 54.92/2.04	TCD_{50}/γ_{50} = 51.87/2.17	TCD_{50}/γ_{50} = 51.97/1.81	TCD_{50}/γ_{50} = 49.12/1.25	*P* value
–10	93.559 ± 0.273	98.584 ± 0.185	99.337 ± 0.093	98.471 ± 0.176	95.929 ± 0.311	0.000
–20	93.528 ± 0.275	98.563 ± 0.187	99.326 ± 0.094	98.451 ± 0.178	95.894 ± 0.314	0.000
–30	93.496 ± 0.277	98.542 ± 0.190	99.316 ± 0.096	98.431 ± 0.180	95.859 ± 0.316	0.000
–40	93.465 ± 0.278	98.521 ± 0.192	99.305 ± 0.097	98.411 ± 0.182	95.823 ± 0.319	0.000
–50	93.433 ± 0.279	98.499 ± 0.194	99.294 ± 0.098	98.390 ± 0.184	95.787 ± 0.321	0.000
–60	93.402 ± 0.281	98.478 ± 0.197	99.283 ± 0.100	98.370 ± 0.186	95.750 ± 0.324	0.000
–70	93.371 ± 0.282	98.456 ± 0.199	99.272 ± 0.101	98.350 ± 0.188	95.715 ± 0.326	0.000
–80	93.340 ± 0.284	98.435 ± 0.202	99.261 ± 0.102	98.329 ± 0.190	95.680 ± 0.329	0.000
–90	93.311 ± 0.285	98.414 ± 0.204	99.251 ± 0.104	98.310 ± 0.193	95.645 ± 0.322	0.000
–100	93.282 ± 0.287	98.394 ± 0.207	99.240 ± 0.105	98.290 ± 0.195	95.612 ± 0.334	0.000

Table 3d TCP comparison of EUD + DV group with different TCD_{50}/γ_{50} values

a value	TCD_{50}/γ_{50} = 36.50/0.72	TCD_{50}/γ_{50} = 54.92/2.04	TCD_{50}/γ_{50} = 51.87/2.17	TCD_{50}/γ_{50} = 51.97/1.81	TCD_{50}/γ_{50} = 49.12/1.25	*P* value
–10	93.64 ± 0.113	98.63 ± 0.072	99.36 ± 0.036	98.52 ± 0.070	96.02 ± 0.126	0.000
–20	93.60 ± 0.122	98.62 ± 0.078	99.35 ± 0.039	98.50 ± 0.070	95.98 ± 0.136	0.000
–30	93.57 ± 0.130	98.60 ± 0.084	99.34 ± 0.042	98.48 ± 0.081	95.95 ± 0.146	0.000
–40	93.54 ± 0.139	98.58 ± 0.090	99.33 ± 0.046	98.46 ± 0.087	95.91 ± 0.156	0.000
–50	93.51 ± 0.147	98.55 ± 0.097	99.32 ± 0.049	98.44 ± 0.093	95.87 ± 0.166	0.000
–60	93.48 ± 0.155	98.53 ± 0.103	99.31 ± 0.052	98.42 ± 0.099	95.84 ± 0.175	0.000
–70	93.44 ± 0.163	98.51 ± 0.109	99.30 ± 0.055	98.40 ± 0.104	95.80 ± 0.185	0.000
–80	93.41 ± 0.170	98.49 ± 0.115	99.29 ± 0.058	98.38 ± 0.110	95.77 ± 0.194	0.000
–90	93.38 ± 0.178	98.47 ± 0.121	99.27 ± 0.061	98.36 ± 0.115	95.73 ± 0.203	0.000
–100	93.36 ± 0.185	98.45 ± 0.127	99.26 ± 0.064	98.34 ± 0.121	95.70 ± 0.211	0.000

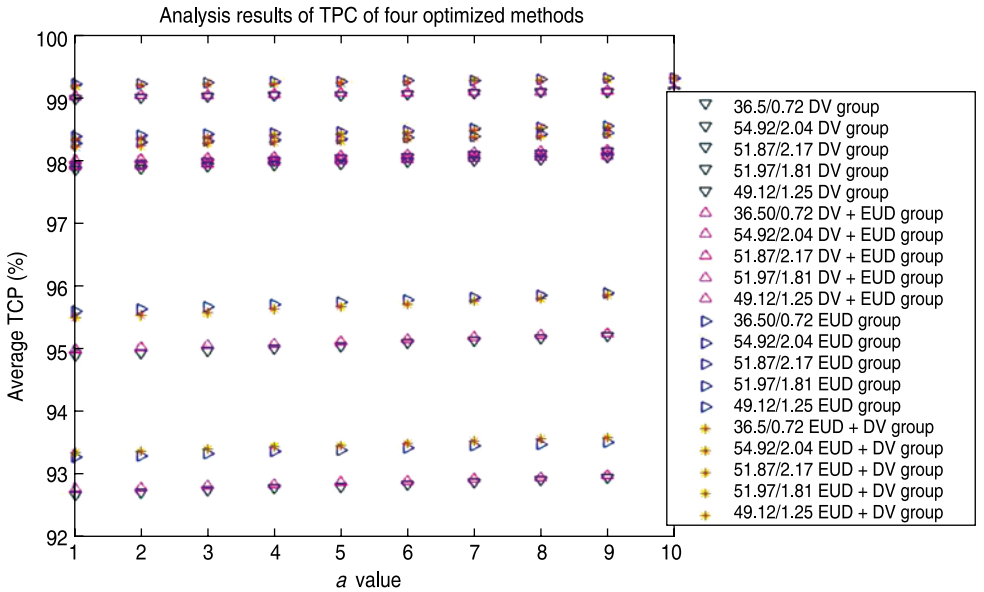

Fig. 1 Results of tumor control probability (TCP) for the four optimization methods

were always higher than those of DV and DV + EUD groups (Fig. 1). It could be seen that the EUD group had an absolute advantage in improving the TCP of the target area and was greatly affected by the value of TCD_{50}/γ_{50}.

Organs at risk

Table 5 shows the dose-volume parameters of OAR. There were no significant differences among the four groups ($P > 0.05$). As shown in Fig. 2, in the range of 0.1 to 1.0, the EUD of normal lung tissue tended to increase with the increase of the *a*-value in the four optimization methods. When the *a*-value was kept unchanged, the EUD mean values of lung tissue demonstrated no obvious difference, except for the EUD + DV group.

This study also compared the number of monitor units

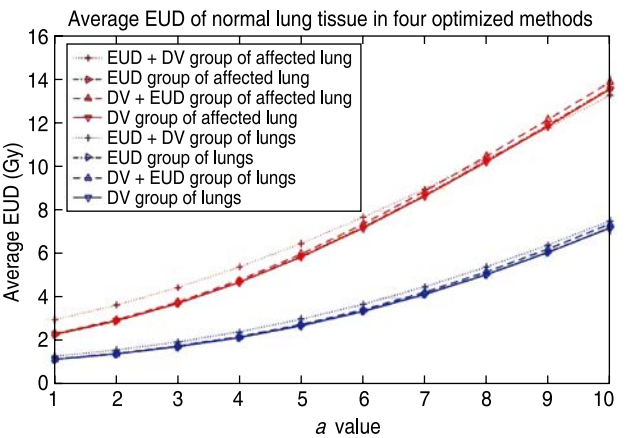

Fig. 2 EUD value of normal lung tissue of the four optimization methods

Table 4 *HI/CI* values for the four plan optimization methods

	DV group	DV + EUD group	EUD group	EUD + DV group	*P* value
HI	0.060 ± 0.008	0.057 ± 0.008	0.072 ± 0.014	0.077 ± 0.015	0.001
CI	0.730 ± 0.063	0.697 ± 0.095	0.703 ± 0.095	0.703 ± 0.088	0.957

Table 5 Dose-volume parameters of OAR under four optimization scenarios

	DV group	DV + EUD group	EUD group	EUD + DV group	*P* value
Lung Dmean (Gy)	5.90 ± 1.135	6.02 ± 1.211	5.91 ± 1.116	5.80 ± 1.036	0.966
Lung V_5 (%)	33.26 ± 8.845	32.82 ± 8.679	34.26 ± 8.959	33.91 ± 8.789	0.983
Lung V_{10} (%)	21.54 ± 4.948	22.02 ± 5.235	21.46 ± 4.668	21.50 ± 5.020	0.994
Lung V_{20} (%)	13.07 ± 2.203	13.54 ± 1.842	13.14 ± 2.240	12.86 ± 2.072	0.908
Lung V_{30} (%)	10.19 ± 1.730	10.74 ± 1.673	10.51 ± 2.019	10.26 ± 2.069	0.908
Heart V_{30} (%)	3.97 ± 8.315	3.19 ± 8.974	3.75 ± 9.620	3.83 ± 9.736	0.998
Heart V_{40} (%)	1.80 ± 4.753	1.68 ± 5.078	1.36 ± 4.215	1.49 ± 4.477	0.997
Heart Dmean (Gy)	2.79 ± 3.068	2.74 ± 3.209	2.74 ± 3.112	2.90 ± 3.277	0.999
Cord Dmax (Gy)	9.23 ± 7.120	9.07 ± 6.682	9.33 ± 6.882	9.79 ± 7.530	0.996

Table 6 Comparison of the MU number and execution time for the four optimization methods

	DV group	DV + EUD group	EUD group	EUD + DV group	*P* value
MU	1808.97 ± 259.33	1799.67 ± 241.27	1387.12 ± 122.66	1450.96 ± 190.26	0.000
Delivery time (min)	3.08 ± 0.397	3.17 ± 0.359	2.45 ± 0.271	2.61 ± 0.341	0.000

(MUs) and plan-delivery time of the four optimization methods. As shown in Table 6, the MUs and delivery time of the EUD and EUD + DV groups were significantly lower than those of the other two groups ($P < 0.05$), showing that using the EUD function for the target area during the optimization was more efficient among the four optimization methods.

Discussion

Since physical optimization is more direct than biological optimization, the dose-volume objective function is more convenient to use in clinical practice [3]. However, the interaction between tissue and X-ray is a very complicated process. The EUD model and the TCP/NTCP model proposed by Niemierko *et al*[2–3, 9] have been considered to be related to the biological characteristics of tissues to some extent. The biological function optimization method based on the above model has some advantages in reflecting the biological response of the tissue to radiation compared to the physical function optimization method. The results of this study showed that the EUD, $D_{2\%}$, $D_{50\%}$, and $D_{98\%}$ of PTV in EUD and EUD + DV groups were higher than those in the other two groups. In other words, the target doses of both groups were generally improved. The authors believe these characteristics of the *a-value* that explain this result.

This study compared the results of four planning optimization methods for 10 patients with NSCLC and found that the EUD and TCP optimized using the biological function were significantly higher than those optimized by the physical function. At the same time, the mean dose of lung tissue was lower and there was a small difference in the dose of heart and spinal cord. This means that, given the same prescription dose and the same constraints, biological function optimization programs can ensure the target area achieves a higher biological effect without increasing the dose on normal tissue. In this way, the therapeutic gain ratio of treatment can be improved to a certain extent, and its advantages can be better reflected in hypofractionated radiotherapy. In addition, through this study, we found that biologically optimized plans are more efficient to implement. Studies have shown that [6], when the EUD function is used for the target area alone, the cold spot is overemphasized in the optimization process, and the constraints on the hotspot are weak. That is to say, in order to keep the dose at each point not lower than the prescription dose, the overall dose in the target area has to be increased, thus the hotspot in the target area tends to be out of control; thus it is not recommended to apply the EUD function alone for the target area during the optimization. In this study, no uncontrollable situation occurred when only the EUD function was used for target area in the optimization. The reason may be that a global hot spot control structure "patient" is used. In this study, five groups of TCD_{50}/γ_{50} values were selected from the study of Okunieff *et al*[9]. In the four optimization methods, although the TCP values reached highest when $TCD_{50}/\gamma_{50} = 51.87/2.17$ is chosen, this combination is more suitable for adenocarcinoma, not for squamous carcinoma. In contrast, $TCD_{50}/\gamma_{50} = 51.97/1.81$ is applicable to all NSCLC cases [9], thus, the value of this combination is recommended for TCP calculations. However, to draw more convincing conclusions, we need to increase the sample size for further study.

In general, compared to the physical optimization, biological optimization has obvious advantages in improving the EUD of the target area and delivery efficiency. This makes the target area achieve a higher biological effect while the irradiated doses of the normal tissue do not increase as a result, being more advantageous in hypofractionated radiotherapy. Mihaylov *et al* [14] conducted a comparative study of physical and biological optimization for prostate cancer cases; it was found that biological optimization significantly increased the target dose while sparing more volumes of OAR. The reason why our results differed from those of some previous studies may be that the same constraints are applied to the same structure in the four optimizations, only the used functions are different, and the differences in the functions themselves may not have obvious influence. In addition, the planners' flexible application ability and experience of various physical and biological functions are also important in embodying the advantages of biological optimization. Nahum *et al* [15] believes that the two-dimensional dose-volume histogram (DVH) data used in the LKB model do not fully represent the dose distribution in three-dimensional space, while the Marsden TCP model also assumes that all clonal cells in each treatment have the same radio sensitivity. Therefore, the currently used biological optimization model only reflects the biological response of different tissues to X-rays to some extent, and there are still some defects and deficiencies. Nevertheless, with the development of technology and

the discovery of more biological optimization models, biological optimization will show more advantages in radiotherapy.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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