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Original Article

Dosimetric differences between intensity-modulated radiotherapy based on equivalent uniform dose and dose-volume optimization in stage III non-small cell lung cancer

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Abstract: Objective: To determine the dosimetric differences between biological and physical functions of equivalent uniform dose (EUD) and dose volume (DV) therapy in patients with phase III non-small cell lung cancer. Methods: Four different radiotherapy plans (DV+DV, DV-EUD+DV, EUD+EUD and EUD-DV+EUD) were developed for 15 patients with stage III NSCLC. To study physical function (DV+DV) the target area was optimized by introducing the conditions of biological function optimization, while the organs at risk were optimized by means of physical function (DV-EUD+DV). Biological function optimization (EUD+EUD) was performed for the target area by applying conditions of physical function optimization while biological function optimization (EUD-DV+DV) was conducted for the organs at risk to compare dosimetric parameters among the four groups of treatment plans. Results: PTV: $D_{2\%}$, $D_{98\%}$, $D_{50\%}$, $V_{105\%}$ and D_{max} of both the DV-EUD+DV group and EDU-DV+EUD group were the minimum (P<0.05). The minimum and average dose of the EUD+EUD group showed an increasing trend and high-dose area became observable. For homogeneity index (HI), DV-EUD+DV group and EUD-DV+EUD results were compared with the other groups (P<0.05), no significant difference was observed statistically between the DV-EUD+DV group and EUD DV+EUD (P=0.659). With regard to conformability index (CI), the results of the four groups showed no significant difference (P>0.05). For the organs at risk, the mean dose of lung tissue (MLD), V_5, V_{10}, V_{20}, V_{30}, heart V_{30}, V_{40}, and D_{mean} also revealed no significant difference (P>0.05). For the spinal cord, the D1 % of the EUD+EUD group and EUD-DV+EUD groups were significantly different (P<0.05) than the other groups. While no significant difference (P=0.32) was found between the EUD+EUD and EUD-DV+EUD groups. When comparing the number of machine unions (MU) no significant difference was revealed (P>0.05) among the results of the 4 groups. Conclusion: The methods featuring optimization of physical and biological functions are effective in improving the uniformity of target area to have better outcome of the treatment. Biological function optimization or the combination of biological and physical function optimization is conducive to significantly reduce the required dose for the spinal cord.

Keywords: Equivalent uniform dose (EUD), non-small cell lung cancer (NSCLC), intensity-modulated radiation therapy (IMRT), biological function, physical function

Introduction

Lung cancer ranks first in the number of new cancer cases and is also a main cause of fatality rates across the world, it accounts for 75% to 80% of lung malignant tumors [1]. The optimization of the intensity modulated radiation therapy (IMRT) plan is frequently based on dose volume (DV) function. Since the optimized parameters are not one-to-one with the interest points of dose volume histogram (DVH) curve, the overall state of dose distribution in the target area is hindered from being effectively regulated. Besides, the dose cold point is possibly a leading cause for the recurrence of tumors within the allowable error range. Proposed by Niemierko et al. in 1997, the concept of equivalent uniform dose (EUD) reflects the function performed by tissue structure and it is an indicator of the nonlinear response

between tumor and dose. Then in 1999, the formula was extended to normal tissues, which means it is a generalized equivalent uniform dose (gEUD) [2, 3]. Recently, studies have focused on the equivalent uniform dose optimization in craniocerebral and abdominal tumors [4-8]. In contrast, there have been very few studies conducted on thoracic tumors, particularly on advanced stage lung cancer. Thus, the current study is purposed to figure out the dosimetric differences between the optimization of biological function based on the equivalent uniform dose and the physical function based on the dose volume for the intensity-modulated radiotherapy intended to treat stage III non-small cell lung cancer.

Materials and methods

Clinical data

Fifteen patients (age 49-94 years) with stage III non-small cell lung cancer who had received radiotherapy in the Xuzhou Central Hospital from 2018 to 2020 were recruited for this study and their localized CT images were collected. Patients were recruited by the following inclusion criteria: 1. the pathological diagnosis result showed non-small cell lung cancer; 2. diagnosed with IIIA-IIIB according to the eighth edition of TNM staging; 3. if patients refused required radiotherapy or inoperable. If patients were unable to fulfill the recruitment criteria or refused to sign the informed consent then they were excluded from the study. The following are major points for exclusion criteria: 1. unable to complete the whole course of radiotherapy due to the patient's own reasons; 2. the patient has severe comorbidities or uncontrollable infections and cannot receive radiotherapy. Among the total recruited 15 patients, 4 patients had stage IIIA and 11 patients at stage IIIB lung cancer. Then, they were divided into 4 groups according to the planning volume target (PTV) and organ at risk (OAR): DV+DV group, DV-EUD+DV group, EUD+EUD group, and EUD-DV+EUD group.

Plan design

The prescription dose of all plans was 60 Gy/30f. For each group of plans, it was required that 100% of the prescription dose of the target area surrounds at least 95% of the target area volume. Considering the possibility that the parameters of planning system as proposed by Senth-ilkumar, et al and Chaikh, et al can affect the planning results, the four groups of plans were redesigned under the Eclipse 13.5 planning system for the purpose of intensity-modulated radiotherapy planning [9, 10]. This system is equipped with two radiotherapy optimization systems: physical and biological functions. For better treatment outcome we designed an optimization model where two functions were combined. All the experimental, sampling and therapeutic protocols were approved by Institutional Board for Ethical Review of Xuzhou Central Hospital, also all the procedures were performed by strictly adhering to the Helsenki declaration of 1964 and its latest amendments. Informed written consent was obtained from all the patients participating in our study.

Calculations

Planning target volume (PTV) was calculated for the 4 groups, including 2% volume dose ($D_{2\%}$), 98% volume dose ($D_{98\%}$), median dose ($D_{50\%}$), maximum dose (D_{max}), the volume exceeding 105% of prescription dose ($V_{105\%}$), homogeneity index (HI) and conformity index (CI). HI closer to "0" indicates a greater level of uniformity. While for CI closer to "1" indicates that it has a better aptamer. The calculation of organ-at-risk involved mean lung dose (MLD), V_5, V_{10}, V_{20}, V_{30}, heart V_{30}, V_{40}, D_{mean}, the dose of 1% volume of spinal cord and computer beating number (MU), of which the MU value indicated that the more complex the plan was, longer the execution process. As shown in (1) and (2) for the calculation formula of HI and CI:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \times 100\% \quad (1)$$

In Equation (1), $D_{2\%}$ represents the maximum dose in the target area, $D_{98\%}$ indicates the minimum dose in the target area, and $D_{50\%}$ denotes the median dose.

$$CI = \frac{V_{T,Pi}}{V_T} \times \frac{V_{T,Pi}}{V_{Pi}} \quad (2)$$

In Equation (2), VT, pi represents the volume of the target region surrounded by the prescribed dose, VT refers to the volume of the target region, and Vpi denotes the volume of the target region surrounded by the prescribed dose.

Table 1. Planned comparison of PTV dose parameters among 15 patients with stage III (stage IIIA, IIIB) non-small cell cnacer in 4 groups ($\bar{x} \pm sd$)

Item	DV+DV	DV-EUD+DV	EUD+EUD	EUD-DV+EUD	P
PTV.D2%	6293.63±54.70	6254.17±57.52	6552.82±142.63	6306.78±105.92	0.000
PTV.D98%	6078.08±69.59	6071.02±40.16	6149.38±113.90	6085.22±50.49	0.000
PTV.D50%	6175.19±38.00	6142.63±35.56	6280.17±107.7	6179.94±59.49	0.000
PTV.V105%	2.65±2.46	1.05±1.28	35.39±26.64	7.52±12.69	0.000
PTV. Dmax	6508.47±124.54	6460.93±107.72	7120.91±436.83	6600.74±184.27	0.000

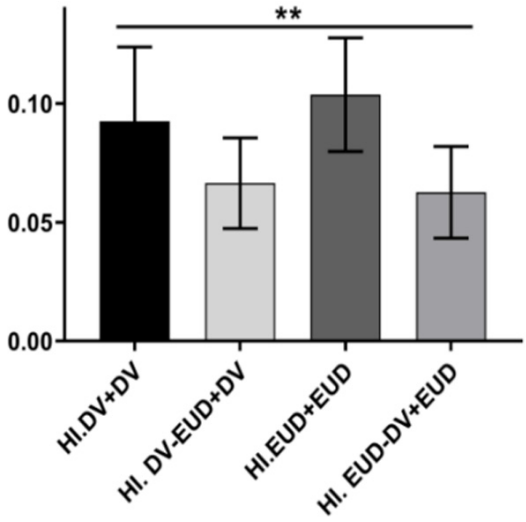

Figure 1. Planned comparison of homogeneity index dose parameters in 4 groups of 15 patients with stage III (stage IIIA, IIIB) non-small cell cnacer. **indicates P<0.01; For HI, being closer to "0" indicates a greater level of uniformity.

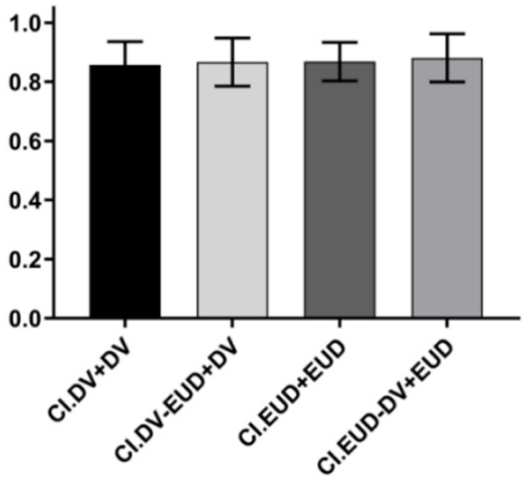

Figure 2. Planned comparison of 4 groups of dose parameters of comfort index in 15 patients with stage III (IIIA, IIIB) non-small cell cnacer. For CI, being closer to "1" indicates that it has a better aptamer. P>0.05.

Statistical methods

One-way analysis of variance was conducted using SPSS 26.0 software. Additionally, in order to visualize the statistical results, some data were presented as a histogram, where P<0.05 indicates a statistically significant difference.

Results

Target area

The statistical results of PTV as shown in **Table 1**, $D_{2\%}$, $D_{98\%}$, $D_{50\%}$, $V_{105\%}$ and D_{max} in the DV-EUD+DV EDU-DV+EUD group were the relative minimum (P<0.05), which was considered to reduce the volume ratio of high dose area and meet the required criteria of the treatment plans. It opened a new possibility to reduce the surrounding normal tissue while increasing the levels of both minimum and average doses. Thus, EUD+EUD could lead to a significant increase in the level of overall dose, especially the maximum dose. The DVH curve shifted to the right, thus resulted into a high dose area which was difficult to reconcile and made it unlikely to meet the actual needs for clinical treatment (**Figure 1**). The DV-EUD+DV group was found superior than two other groups in the uniformity of target, while the results of DV-EUD+DV EUD-DV+EUD group showed similarity while no significant difference was observed (P=0.659). The statistical results of deformability index (CI) are shown in **Figure 2**, which revealed that the four groups have a similar pattern therefore no significant difference was noted (P>0.05).

Organ at risk

The results of lung tissue exposure are detailed in **Figure 3**. As revealed by data analysis, the four groups had a similar pattern, and no significant difference was found among all groups (P>0.05). However, the exposure of normal lung

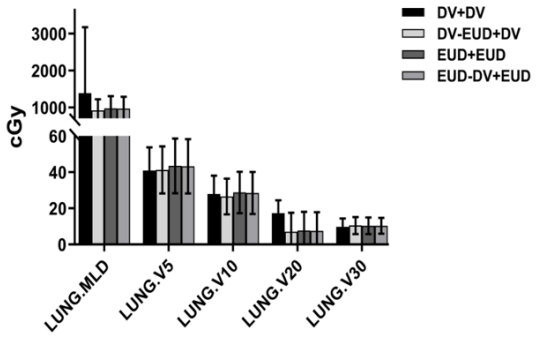

Figure 3. Planned comparison of lung tissue dose parameters in 15 patients with stage III (IIIA, IIIB) non-small cell cnacer in 4 groups.

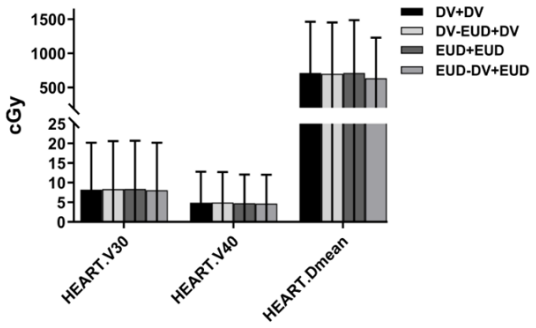

Figure 4. Planned comparison of cardiac dose parameters in 15 patients with stage III (IIIA, IIIB) non-small cell cnacer in 4 groups.

tissue in the DV-EUD+DV group was slightly lower than the other three groups. **Figure 4** showed the statistical results of heart exposure dose. From this figure, it could be seen that the four groups produced similar planning results, with no significant difference (P>0.05). As shown in this **Figure 5**, the EUD+EUD-DV+EUD group was significantly better than two other groups. More specifically, there was a significant reduction to spinal cord exposure (P<0.05). The machine beating number (MU) was shown to be similar among the four groups, and the difference showed no statistical significance (P>0.05) **Figure 6**.

Discussion

Commonly used physical optimization is easy to understand and easy to use. At present, most of the radiotherapy plans are commonly adopting this approach of optimization. Despite its capability to meet the requirements of the clinical treatment, it remains subject to various

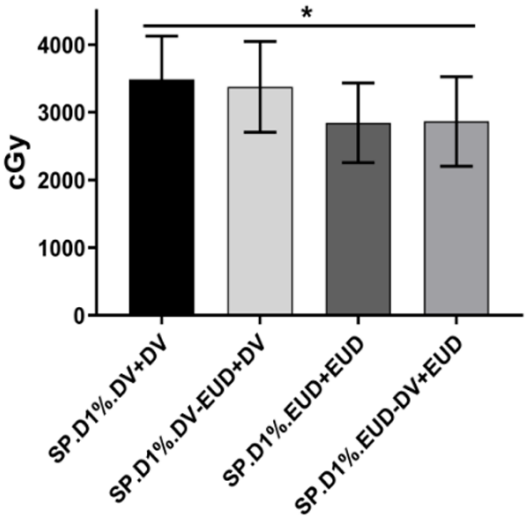

Figure 5. Planned comparison of spinal cord (SP) dose parameters in 15 patients with stage III (IIIA, IIIB) non-small cell cnacer in 4 groups (Mean ± SD). *indicates P<0.05.

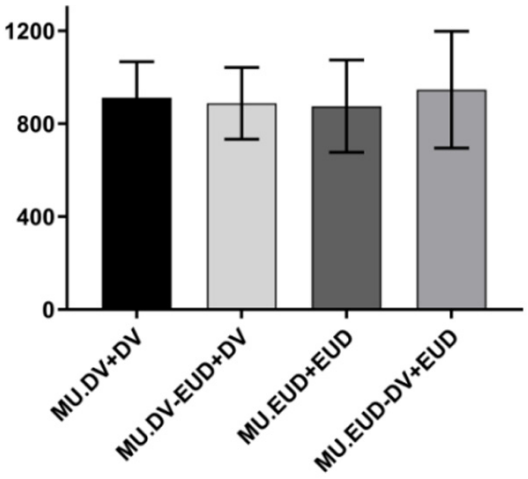

Figure 6. Planned comparison of MU parameters in 15 patients with stage III (IIIA, IIIB) non-small cell cnacer in 4 groups (Mean ± SD). A larger number indicates a more complex plan.

constraints and requires a heavy workload of plan iteration calculation. In addition, often in clinical practice cases appears when the given dose volume constraint is not available or a feasible solution, but it is not considered as the optimal solution. Proposed by Niemierko et al, the equivalent uniform dose function reflects the function of tissue structure and can be used to address the defects of physical function on a certain basis. It has now been confirmed that the EUD-based optimization meth-

od intended for the organs at risk can reduce the level of normal tissue acceptance while ensuring the target dose, which allows patients to achieve a higher treatment gain ratio [11-21]. Its generalized formula is expressed as follows:

$$gEUD = \left(\sum_i V_i D_i^a\right)^{1/a}$$

In the formula, Di represents the dose of the i^{th} voxel, v_i indicates the volume of the i^{th} voxel within the irradiated area, and a denotes a characteristic parameter of the tumor or normal tissue. Theoretically, "a" can take on any value. In general, for tumor tissues, "a" takes on a larger negative value, a >1 is applicable to "tandem organs" (such as heart, spinal cord, etc.), and a =1 is applicable to "parallel" organs (such as lung tissues, etc.) [22].

In this study, it was found that performing EUD optimization alone in the target area would shift the DVH curve to the right as a whole, and it is unlikely to make a satisfactory optimization plan by replacing different "a" values. It is believed in this paper that the reason for the poor control on dose hotspots caused by EUD optimization alone lies in the fact that the design of equivalent uniform dose model was premised on the statistical model of Poisson distribution, and it's mathematical basis are power law dependent on the response of the complex biological systems to radiation. The target cell hypothesis and the cell killing theory is that to give sufficient dose to the tumor; which leads to an increase in the overall dose requirements of the target area while increasing the minimum dose or average dose the uniformity of the target area could not be covered. As for the target area, the optimization mode combining the optimization of physical function and biological function was adopted to reduce the high dose area while developing a treatment plan with a better uniformity for the target area, which is conducive to reducing the acceptance of organs at risk through a better space. Given that the subjects of this study were stage III NSCLC, one case of nasopharyngeal carcinoma, one case of cervical cancer and one case of rectal cancer, were selected to conduct simple EUD optimization, so as to verify whether the practice of simple EUD optimization in the target area could produce similar results for the malignant tumors at other sites. According to the results, there were still some dose hotspots that were difficult to regulate when the biological optimization plan was carried out alone in the target area. Due to the small number of cases and the lack of strict screening imposed on the selected cases, it was potentially contributory to the formation of hot spots. In addition, due to strict control of normal lung tissue and heart exposure at the start of the plan, the level of lung and heart exposure was low, which is a potential reason for the insignificant difference shown between the four groups. It is worth mentioning that EUD optimization can play a positive role in protecting the spinal cord and significantly reducing the exposure dose to the spinal cord. In addition, due to the significant differences in the location and shape of stage III lung cancer and tumor volume, as well as the small number of cases, it is impractical for the advantages of biological optimization to be fully demonstrated. A large scale study is also necessary to increase the number of cases to obtain more reliable results.

In summary, through the aforementioned study, it is believed that for stage III non-small cell lung cancer patients undergoing radical radiotherapy, it is recommended to combine physical optimization and biological optimization for the target area. While for the organs at risk, it is recommended to perform biological optimization or combine with physical optimization. We standardized that the optimization method based on equivalent uniform dose function have promising results. With the establishment of more functional models and the improvement of the mathematical foundation, biological optimization will attract increasing attention for intensity-modulated radiotherapy.

Disclosure of conflict of interest

None.

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