Reducing dose to the lungs through loosing target dose homogeneity requirement for radiotherapy of non small cell lung cancer

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Abstract
It is important to minimize lung dose during intensity-modulated radiation therapy (IMRT) of nonsmall cell lung cancer (NSCLC). In this study, an approach was proposed to reduce lung dose by relaxing the constraint of target dose homogeneity during treatment planning of IMRT. Ten NSCLC patients with lung tumor on the right side were selected. The total dose for planning target volume (PTV) was 60 Gy (2 Gy/fraction). For each patient, two IMRT plans with six beams were created in Pinnacle treatment planning system. The dose homogeneity of target was controlled by constraints on the maximum and uniform doses of target volume. One IMRT plan was made with homogeneous target dose (the resulting target dose was within 95%–107% of the prescribed dose), while another IMRT plan was made with inhomogeneous target dose (the resulting target dose was more than 95% of the prescribed dose). During plan optimization, the dose of cord and heart in two types of IMRT plans were kept nearly the same. The doses of lungs, PTV and organs at risk (OARs) between two types of IMRT plans were compared and analyzed quantitatively. For all patients, the lung dose was decreased in the IMRT plans with inhomogeneous target dose. On average, the mean dose, V5, V20, and V30 of lung were reduced by 1.4 Gy, 4.8%, 3.7%, and 1.7%, respectively, and the dose to normal tissue was also reduced. These reductions in DVH values were all statistically significant (P < 0.05). There were no significant differences between the two IMRT plans on V25, V30, V40, V50 and mean dose for heart. The maximum doses of cords in two type IMRT plans were nearly the same. IMRT plans with inhomogeneous target dose could protect lungs better and may be considered as a choice for treating NSCLC.

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KEY WORDS
IMRT, non small cell lung cancer, plan optimization, target dose homogeneity, treatment planning
INTRODUCTION

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer death among males. About 85% of lung cancers are NSCLC worldwide.\(^1\) Radiotherapy plays an important role in the treatment of locally advanced, unresectable NSCLC.\(^2\) Treatment outcome of standard radiotherapy for NSCLC patients has not improved much during the past decades, and the 5-year relative survival rate is still no more than 20%.\(^3\) Local failure often occurs in the primary tumor. Doses higher than the standard 60–66 Gy are required to obtain a better local tumor control.\(^4,5\) But this is limited by the protection of organs at risk. Some patients suffered from severe side effects after radiation therapy.\(^6,7\) Radiation pneumonitis (RP) is the main dose-limiting complication in radiation therapy for NSCLC, and occurs in 5%–50% of patients.\(^8,9\) In the case of conventionally fractionated radiotherapy, the traditional strategy for minimizing patients’ risk is to follow empirically established dose-volume constraints, such as V20 < 30%–35% and mean lung dose (MLD) < 20–23 Gy. However, the relationship between RP risk and dosimetrical statistics such as MLD varies among institutions. And it also changes when different treatment techniques (i.e., CRT, IMRT, and VMAT) are applied.\(^10\)

IMRT is a common technology for the treatment of lung cancer.\(^11\) The target volume could get higher dose and better conformity index than 3D-CRT. However, the improvement of uniformity of target dose could increase the volume of the low dose area in nearby OARs. As a result the volume of low dose area in the lung could be significantly increased.\(^12,13\) Shirvani et al found that the proportion of patients under IMRT treatment increased year by year and V20 of lung decreased significantly in IMRT group based on 3986 patients. Compared with 3D-CRT group the adverse reaction of lung occurred at similar rates using IMRT and showed that the lower V20 did not reduce the incidence of RP.\(^14\) The reason may be that V5 of lung would be increased as IMRT applied.\(^15\) To minimize the risk of RP some new techniques were introduced to reduce the lung dose, including respiratory gated PET/CT, Cyber Knife, VMAT, etc.\(^16–19\)

Conventionally, the standard practice is that tumors should be irradiated to an intended uniform, or homogeneous, dose.\(^20\) While this optimizes the tumor control probability in the case of homogeneous tumors, this is generally not the optimal dose distribution in tumors with spatial variation in radiation sensitivity.\(^21\) In addition, dose escalation strategies that involve delivery of uniform doses are typically limited by normal tissue dose tolerance. There have been studies indicating that deliberately using nonuniform radiation doses allows for dose escalation of tumor subvolumes without necessarily increasing the dose which is delivered to adjacent critical structures.\(^22,23\)

It still remains unclear whether the dose to OARs could be reduced when the dose nonuniformity in the target area is increased. The goal of this study is to investigate whether it is beneficial to decrease the lung toxicity for NSCLC by increasing target dose inhomogeneity in IMRT plans.

METHODS

2.A Patient data

10 NSCLC patients with lung tumor on the right side treated at our institution between July 2014 and October 2015 were selected in this study which had been approved by ethics committee. The patient-related privacy information (e.g., name, identification number, telephone number) has been removed. All the patients were immobilized in the supine position using a thermoplastic mask. Treatment plans were made based on computed tomography (Philips, Brilliance Big Bore) with slice thickness of 3 mm.

The gross tumor volume (GTV) was delineated by experienced radiation oncologists based on the planning CT (free-breathing scan) with fluorodeoxyglucose positron emission tomography (FDG-PET) images as auxiliary references, and consisted of the primary tumor and involved lymph nodes. The clinical target volume (CTV) was created as an expansion of the GTV by 10 mm in mediastinum and 5 mm in lung tissue excluding bony structures and major vessels in accordance with recommendations provided by the Danish Oncology Lung cancer Group (DOLG). The planning target volume was created as a patient specific expansion of the CTV with a margin of 5–10 mm.\(^24,25\) The organs at risk included the heart, the spinal cord, the lungs, and the normal tissues. The prescribed dose was 60 Gy in 2.0 Gy daily fractions.

### Table 1 Summary of patient characteristics.

| Patient No. | Age | TNM  | PTV Volume (cm³) |
|-------------|-----|------|-----------------|
| 1           | 35  | T2N3M0 | 392.9          |
| 2           | 73  | T3N2M0 | 403.1          |
| 3           | 47  | T2N1M0 | 210.8          |
| 4           | 60  | T2N2M0 | 227.5          |
| 5           | 77  | T3N1M0 | 273.4          |
| 6           | 55  | T2N3M0 | 381.0          |
| 7           | 40  | T2N1M0 | 212.9          |
| 8           | 69  | T2N1M0 | 225.3          |
| 9           | 57  | T2N2M1 | 251.6          |
| 10          | 56  | T3N2M0 | 395.8          |

2.B Plan optimization

The IMRT plans were made on Pinnacle 9.10 workstation and treated on Elekta Synergy accelerator using 6 MV photon beams. The adaptive convolution algorithm provided by Pinnacle was chosen as the dose calculation engine and the calculation grid resolution was set as $2 \times 2 \times 2$ mm³. The dose of treatment plans was calculated on free-breathing CT. Two IMRT plans using a static step-and-shoot delivery approach were created for each patient. One was with standard homogeneous dose distribution (IMRT\(_{\text{hom}}\)) for target, and the other was with an inhomogeneous dose distribution (IMRT\(_{\text{inh}}\)) for...
target. The two IMRT plans used the same couch and collimator angles, and consisted of six beams with the gantry angles 185°, 215°, 245°, 345°, 15°, and 155° respectively.

For IMRT_homo plans, PTV dose was restricted within 95%–107% of the prescribed dose (60 Gy) based on the recommendation of International Commission on Radiation Units. The maximum dose of spinal Cord PRV (planning organ at risk volume) was 45 Gy, \( V_{20 \text{ Gy}} \), and mean dose of the lungs were set to be as low as possible. The homogeneity of the PTV was enforced by increasing the weight of the PTV uniform dose to 100. For IMRTinho plans, the dose constraints were: PTV dose \( \geq 95\% \) of the prescribed dose (60 Gy), maximum dose of 45 Gy to the spinal Cord PRV, \( V_{20 \text{ Gy}} \), and mean dose for the lungs were set to be as low as possible. There were no uniform dose constraints for PTV. For each patient, a “Boost” optimization region was constructed by expanding the GTV with the same expansion margin. There were no limitations on the maximum dose to this region. Details of objectives set for the initial optimization were illustrated in Table 2.

The additional contours were as follows: (a) PTV-3 mm, shrinkage from the PTV by 3 mm; (b) Ring1 and Ring2, the 5-mm-wide rings at 5 mm and 10 mm distance, respectively, from the PTV; (c) Normal Tissue, the whole CT volumes excluding the PTV expanded by 20 mm in all directions; (d) Boost, GTV expanded by 2 mm in all directions; (e) PTV-Boost, the volume of PTV excluding Boost.

### Table 2 Objective settings for the initial optimization.

| Item | ROI name | Group | Objective type | Target(Gy) | Weight |
|------|----------|-------|----------------|------------|--------|
| 1    | PTV      | IMRT_homo | Maximum dose   | 63         | 50     |
|      | PTV-Boost| IMRTinho | Maximum dose   | 63         | 50     |
| 2    | PTV      | IMRT_homo | Uniform dose   | 60.5       | 100    |
|      | IMRT_homo| /      | /              | /          | /      |
| 3    | PTV      | Both    | Minimum dose   | 59.5       | 90     |
| 4    | PTV      | Both    | Minimum DVH    | 60/95% coverage | 100     |
| 5    | PTV-3 mm | Both    | Minimum dose   | 60         | 30     |
| 6    | Lung     | Both    | Maximum DVH    | 5/44% coverage | 30     |
| 7    | Lung     | Both    | Maximum DVH    | 20/18% coverage | 60     |
| 8    | Lung     | Both    | Maximum DVH    | 30/14% coverage | 30     |
| 9    | Lung     | Both    | Maximum EUD    | 11         | 1      |
| 10   | Cord     | Both    | Maximum dose   | 35         | 40     |
| 11   | Cord PRV | Both    | Maximum dose   | 38         | 60     |
| 12   | Cord PRV | Both    | Maximum EUD    | 7          | 0.5    |
| 13   | Heart    | Both    | Maximum DVH    | 30/18% coverage | 30     |
| 14   | Heart    | Both    | Maximum DVH    | 40/13% coverage | 30     |
| 15   | Heart    | Both    | Maximum EUD    | 15         | 0.3    |
| 16   | Ring1    | Both    | Maximum dose   | 59         | 20     |
| 17   | Ring2    | Both    | Maximum dose   | 56         | 20     |
| 18   | Normal Tissue | Both | Maximum dose | 50         | 20     |
| 19   | Normal Tissue | Both | Maximum EUD | 10         | 0.2    |

Minimum DVH 60/95% coverage: the minimum normalized volume that is radiated by a dose greater than 60 Gy is 95%; Maximum DVH 5/44% coverage: the maximum normalized volume that is radiated by a dose greater than 5 Gy is 44%.

#### 2.C Plan evaluation

IMRT_homo and IMRTinho plans were considered acceptable if at least 95% of PTV volume receiving 100% of the prescribed dose. All plans were reviewed and evaluated by one experienced radiation oncologist according to the standard clinical protocol. To quantify the target coverage and dose distribution, various dosimetric metrics were applied as follows: (a) \( D_{2\%} \) defined as the maximum dose for the PTV and indicated the maximum dose; (b) conformity index (CI) and homogeneity index (HI); (c) total number of monitor units; (d) mean dose. For a fair comparison, we normalized IMRT_homo and IMRT_homo plans to the same level of \( D_{98\%} \) of PTV. Organs at risk were evaluated in terms of the \( D_{\text{mean}} \) and percent of volumes receiving different doses. The percent of volumes \( V_{5}, V_{10}, V_{15}, V_{20}, V_{30}, V_{40}, V_{50} \), and \( D_{\text{mean}} \) for Lungs and \( V_{25}, V_{30}, V_{40}, V_{50} \), and \( D_{\text{mean}} \) for heart were recorded. The maximum dose and \( D_{\text{mean}} \) for cord, cord PRV and normal tissue were also recorded. A margin of 5 mm was added to cord to form the cord PRV.

Normal tissue complication probabilities (NTCP) model was used to evaluate the treatment plans. The model was based on the Lyman–Kutcher–Burman (LKB) model in this study. LKB model is defined with the following equations: 27
NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \quad (1)

m = \frac{D_{\text{eff}} - TD_{50}}{mTD_{50}} \quad (2)

D_{\text{eff}} = \left( \sum v_i D_i^{1/n} \right)^n \quad (3)

where $D_{\text{eff}}$ is the dose that, if given uniformly to the entire volume, will lead to the same NTCP as the actual nonuniform dose distribution, $TD_{50}$ is the uniform dose given to the entire organ volume that results in 50% complication risk, $m$ is the slope of the curve represented by the integral of the normal distribution, $n$ is a parameter which describes the magnitude of the volume effect, $v_i$ is the relative volume related to dose voxel $D_i$. In this calculation, $TD_{50} = 24.5$ Gy, $m = 0.18$, and $n = 0.87$ for lung which is given by Pinnacle planning system. All the results were analyzed using the paired $t$-test. A $P$-value of less than 0.05 was considered statistically significant. SPSS software (IBM SPSS Statistics, version 22) was used for the analyses.

3 | RESULTS

For all patients, both IMRT$_{\text{homo}}$ and IMRT$_{\text{inho}}$ plans were accepted for clinical treatment by the radiation oncologist. Figures 1 and 2 were the comparisons of dose distributions and dose–volume histograms between two plans for one patient. They showed that the

**Fig. 1.** Isodose distribution of IMRT$_{\text{inho}}$ (a, b, c) and IMRT$_{\text{homo}}$ (d, e, f) plans for one patient with six coplanar beams.

**Fig. 2.** Dose–volume histograms (DVH) for (a) PTV and Lung (b) Heart, Cord, Cord PRV, and NT obtained with IMRT$_{\text{inho}}$ and IMRT$_{\text{homo}}$ plans.
uniformities of PTV dose of two plans were different. It was also clear that the mean dose of lung in IMRTinho plan was lower than that in IMRT homo plan, while the doses of the other OARs in IMRTinho plans were nearly the same as those in IMRT homo plans.

The dosimetric statistics of PTV in the two IMRT plans were listed in Table 3. IMRT homo exhibited better HI than IMRTinho (P = 0.001). D2%, Mu and mean dose showed significant difference with P < 0.001, P = 0.001, and P < 0.001 respectively. There were no significant differences for D98%(P = 0.876), CI (P = 0.176), number of segments (P = 0.364), and delivery time (P = 0.094) when comparing IMRT homo plans with IMRTinho plans.

The dosimetric statistics of OARs in the two IMRT plans were listed in Table 4. The mean volume of lungs in this study was 3013.3 cm³ (ranged from 2571.4 to 4892.3 cm³). Lung dose in IMRTinho plans was significant reduced. V20 of lungs decreased from 27.9 ± 3.8% (IMRT homo) to 24.2 ± 3.1% (IMRTinho) with P < 0.001, and the MLD decreased from 15.7 ± 2.1 Gy (IMRT homo) to 14.3 ± 2.0 Gy (IMRTinho) (P < 0.001). On average, V5 of lungs decreased from 57.1 ± 8.3% (IMRT homo) to 52.3 ± 8.0% (IMRTinho). V10 of lungs decreased from 42.6 ± 7.1% (IMRT homo) to 38.2 ± 6.8% (IMRTinho), and V30 of lungs decreased from 19.6 ± 2.4% (IMRT homo) to 17.9 ± 2.4% (IMRTinho). Other dose-volume statistics such as V15, V40, and V50 in IMRTinho plans also showed significant decreases while comparing with those in IMRT homo plans. Figure 3 showed averaged difference of dose-volume histograms (IMRT homo − IMRTinho) for lungs with standard deviation. The peak of averaged difference was 5.5% corresponding to the dose of 4 Gy in the low dose area.

For heart, the differences of V25, V30, V40, and V50 between IMRT homo and IMRTinho plans were within 0.6%, and all the P values of statistical parameters were more than 0.05. Therefore, there were no significant differences between the IMRT homo and IMRTinho plans on V25, V30, V40, V50 and mean dose. As to cord and cord PRV, the maximum dose were 37.7 ± 5.0 Gy and 42.1 ± 4.1 Gy in IMRT homo plans, while those were 37.6 ± 5.8 Gy and 42.9 ± 4.7 Gy for IMRTinho plans. And the P values were 0.860 and 0.273, indicating the maximum dose of cord and cord PRV in the both plans had no significant difference. For normal tissue, IMRTinho plans showed lower doses than IMRT homo plans. The mean doses in the two plans were 12.0 ± 1.2 Gy and 11.2 ± 1.3 Gy with P = 0.002.

**Table 3** Dosimetric parameters comparison of homogeneous and inhomogeneous plans for PTV (mean ± standard deviation).

| Organ at risk | IMRT homo | IMRTinho | P-value |
|---------------|-----------|----------|---------|
| V5 (%)        | 57.1 ± 8.3| 52.3 ± 8.0| 0.005   |
| V10 (%)       | 42.6 ± 7.1| 38.2 ± 6.8| 0.002   |
| V15 (%)       | 34.4 ± 5.7| 29.9 ± 4.5| <0.001  |
| V20 (%)       | 27.9 ± 3.8| 24.2 ± 3.1| <0.001  |
| V30(%)        | 19.6 ± 2.4| 17.9 ± 2.4| <0.001  |
| V40 (%)       | 14.2 ± 2.4| 13.1 ± 2.7| 0.001   |
| V50 (%)       | 9.5 ± 2.7 | 8.7 ± 2.9 | 0.001   |
| Mean (Gy)     | 15.7 ± 2.1| 14.3 ± 2.0| <0.001  |
| NTCP          | 4.2 ± 1.5 | 2.5 ± 1.2 | <0.001  |

**Table 4** Dosimetric parameters comparison between homogeneous and inhomogeneous plans for organs at risk (mean ± standard deviation).

| Organ at risk | IMRT homo | IMRTinho | P-value |
|---------------|-----------|----------|---------|
| Lung          |           |          |         |
| V5 (%)        | 57.1 ± 8.3| 52.3 ± 8.0| 0.005   |
| V10 (%)       | 42.6 ± 7.1| 38.2 ± 6.8| 0.002   |
| V15 (%)       | 34.4 ± 5.7| 29.9 ± 4.5| <0.001  |
| V20 (%)       | 27.9 ± 3.8| 24.2 ± 3.1| <0.001  |
| V30(%)        | 19.6 ± 2.4| 17.9 ± 2.4| <0.001  |
| V40 (%)       | 14.2 ± 2.4| 13.1 ± 2.7| 0.001   |
| V50 (%)       | 9.5 ± 2.7 | 8.7 ± 2.9 | 0.001   |
| Mean (Gy)     | 15.7 ± 2.1| 14.3 ± 2.0| <0.001  |
| NTCP          | 4.2 ± 1.5 | 2.5 ± 1.2 | <0.001  |
| Heart         |           |          |         |
| V25(%)        | 25.1 ± 10.6| 24.5 ± 12.3| 0.543   |
| V30(%)        | 21.6 ± 9.3 | 21.3 ± 10.8| 0.687   |
| V40(%)        | 14.4 ± 6.4 | 14.9 ± 8.4 | 0.662   |
| V50(%)        | 8.7 ± 4.2  | 9.1 ± 5.7  | 0.733   |
| Mean (Gy)     | 16.1 ± 5.8 | 16.0 ± 7.0 | 0.869   |
| Cord          |           |          |         |
| Max (Gy)      | 37.7 ± 5.0 | 37.6 ± 5.8 | 0.860   |
| Cord PRV      | 42.1 ± 4.1 | 42.9 ± 4.7 | 0.273   |
| Normal tissue |           |          |         |
| Mean (Gy)     | 12.0 ± 1.2 | 11.2 ± 1.3 | 0.002   |

**Fig. 3.** Averaged difference of dose-volume histograms (IMRT homo − IMRTinho) for lung with standard deviation. The standard deviation has been drawn as lines with fill area.
4 | DISCUSSION

Nielsen et al have used inhomogeneous dose distributions as a way to increase tumor control probability. The goal of this study was to investigate if increasing target dose inhomogeneity could be beneficial to decrease the lung toxicity for NSCLC using IMRT plans. For this purpose, IMRT_{homo} plans were developed with no uniform dose constraints for PTV and no maximum dose constrains for GTV. As shown in Table 3, CIs of the two IMRT plans were nearly the same and HIs were significantly different. For IMRT_{homo} plans mean dose to the PTV was 62.3 ± 0.7 Gy, whereas for IMRT_{inho} plans that was 66.0 ± 1.9 Gy. In certain cases, IMRT_{inho} plans could increase the dose to tumor. Although the increased dose was only about 3.7 Gy, it might be beneficial to improve local control of tumor.

The correlation between severe RP and MLD was reported by several authors. In a planning study by Murshed, it was suggested that if MLD was decreased by 2 Gy the risk of RP could be reduced by 10%. It was reported that introducing V5 constraint could significantly decrease the lethal pneumonitis. Claude et al showed that only MLD, V20 and V30 were predictive of the severe RP. They suggested that a large panel of thresholds from low to high dose could provide advantages.

The result shown in Fig. 3 and Table 4 suggested that lower lung dose values and NTCP could be obtained from low to high dose region in the IMRT_{inho} plans. Relaxing target dose homogeneity could lead to a significant reduction (3.7% absolute difference) in the lung volume receiving doses <20 Gy which was in the low dose region. IMRT_{inho} plans showed an average decrease of V5 with 4.8% absolute difference compared with IMRT_{homo} plans. Therefore, decreased volume of lung was irradiated at low dose area. In the high dose region, IMRT_{inho} plans could give a dose reduction to lung by about 10%. So the risk of radiation pneumonitis could potentially be decreased. The mean dose, V30 and V40 were often used as...
indicators for heart toxicity. The equal heart toxicity was expected for both homogeneous and inhomogeneous plans in this study because their mean dose, V30 and V40 were similar. The maximum dose of cord and cord PRV in the two plans were kept similar. While lung dose reduced, normal tissues dose was also decreased in IMRT_{inho} plans. This study demonstrated that reducing dose to lungs was possible without increasing the dose to the other OARs.

The esophagus was often located close to or may be part of the target volume. In this case, plan optimization might lead to high dose at the esophagus which must be avoided by adding more constraints to restrict it. The hot spots which were close to cord should be paid special attention and these hot spots should be avoided as possible in the process of plan optimization. The impact of daily setup errors on dose distribution was estimated by modifying the position of the isocenter point on planning CT slices of one patient. Six plans with same beamlets and MUs of IMRT_{inho} were created, and the prescribed dose was 10 Gy in 2.0 Gy daily fractions for each plan. Isocenter was shifted toward the head, foot, left, right, anterior, and posterior, respectively, by 5 mm in each plan. The total “estimated” plan (IMRT_{inho}+5 mm) was composed of the six plans. Dose distribution between IMRT_{inho}+5 mm and IMRT_{inho} plans was compared as shown in Fig. 4. We can see that the position of hot spots remains unchanged and big hot spots become smaller due to edge blurring effect from the Fig. 4. Some small hot spots that appear in IMRT_{inho} plan don’t manifest in the dose distribution received by the patient due to day to day setup variations. There is little change in lung and GTV doses between IMRT_{inho} plans and IMRT_{inho}+5 mm plans as shown in Fig. 5.

Respiratory motion and tumor shrinkage throughout treatment can further affect the dose to the tumor and the hot spots may move toward nearby critical structures. The use of daily localization with CBCT could detect changes in the target and ensure the safety of OARs. As the spatial distribution of biological properties in tumors such as proliferation and hypoxia are known to be nonuniform, the dose distribution that maximizes tumor control probability for a given tumor is also nonuniform. Regions of high radiosensitivity may correspond to regions of high tumor proliferation, whereas regions of high radioresistance may correspond to regions of tumor hypoxia. Based on positron emission tomography images and IMRT_{inho} plans, these regions might be controlled to get inhomogeneous dose distribution to increase tumor control probability. Besides NSCLC, this method should be valid in other cancers such as esophageal cancer, liver cancer, etc., which will be investigated in the future studies.

5 | CONCLUSION

It was demonstrated that relaxing the constraints on maximum and uniform dose in the target volume could significantly reduce the dose to lungs from low to high dose region. With this approach, the risk of radiation pneumonitis could potentially be decreased. In addition, it could increase the mean dose to tumor, which might be beneficial to improve local control of tumor by radiotherapy. IMRT plans with inhomogeneous target dose could protect lungs better and may be considered as a choice for NSCLC treatment.

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CONFLICT OF INTEREST

All authors approved the final manuscript, and declared that they have no potential conflicts of interest to this work.

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