Original Research Article

Harmonization of dose prescription for lung stereotactic radiotherapy

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• PTV-based prescription

A B S T R A C T

Background and purpose: Pulmonary stereotactic treatments can be performed using dedicated linear accelerators as well as robotic-assisted units, and different strategies can be used for dose prescription. This study aimed to compare the doses received by the tumor with a gross tumor volume (GTV)-based prescription on D98%GTV using a robotic-assisted unit (method A) and planning target volume (PTV)-based prescription on D95%PTV using a dedicated linac (method B).

Material & methods: Plans of 32 patients were collected for method A, and a dose of 3 × 18 Gy was prescribed using type A algorithm and recalculated using a Monte-Carlo (MC) algorithm. The plans were normalized to match D98%GTV with the mean D98%GTV of the cohort. The plans of 23 patients were collected for method B, and a dose of 3 × 18 Gy was prescribed to D95%PTV using a MC algorithm. A 4D-sum method was developed to estimate doses for PTV and GTV. For validation, all plans were recalculated using an independent MC double-check software. A dose harmonization on D95%GTV was determined for both methods.

Results: For method A, mean doses were D98%GTV = 59.9 ± 2.1 Gy, D95%GTV = 55.6 ± 1.2 Gy, and D95%GTV = 49.5 ± 0.0 Gy. For method B, the reported doses were D98%GTV = 64.6 ± 2.1 Gy, D95%GTV = 62.8 ± 1.7 Gy, and D95%GTV = 60.0 ± 1.7 Gy. The dose trade-off of D98%GTV = 55 Gy was obtained for both methods. For method A, it corresponded to a dose prescription of 3 × 20 Gy using type A algorithm, followed by rescaling to obtain D98%GTV = 55 Gy. For method B, it corresponded to a dose prescription of D95%PTV = 3 × 16.5 Gy using the MC algorithm.

Conclusions: This study determined similar near-minimum doses D95%GTV of approximately 3 × 18.3 Gy (55 Gy) using a GTV-based prescription on a robotic-assisted unit (method A) and a PTV-based prescription on a dedicated linac (method B).

1. Introduction

Stereotactic body radiotherapy (SBRT) is used to irradiate non-small cell lung cancer (NSCLC) cells in the early stages. It allows a high tumor control with contained toxicity [1]. The main challenges associated with pulmonary SBRT are related to tumor motion during the breathing cycle and variations in the tissue densities of the lungs, tumors, and surrounding organs at-risk. These challenges necessitate the use of specific strategies at each step of radiotherapy treatment, and multiple methods of dose prescription have been reported.

In 2017, the ESTRO-ACROP survey [2] has revealed a consensus for a dose prescription of 3 × 15 Gy to D95% planning target volume (PTV). However, in case of pulmonary tumors, the gross tumor volume (GTV) is surrounded by tissues of low densities and as reported in literature [3], prescribing a dose to PTV in lung SBRT is equivalent to prescribing a dose in the air. To overcome this, Lacornier et al. [3] proposed prescribing doses to an indicator of GTV, D50% or D98%; this method is described in ICRU 91 [4].

Patients with NSCLC can be treated using SBRT on a robotic-assisted platform while tracking the tumor motion (no internal target volume [ITV]) in a two-view mode [5]) or on dedicated linear accelerator (linac) with ITV strategy. Chan et al. [6] compared the differences between these two treatment techniques by generating plans using the Monte Carlo (MC) algorithm at a dose of D95%PTV = 48 Gy (in six fractions) and showed that the doses D99% GTV in the plans generated using the robotic-assisted unit were higher by approximately 3.0 % than those generated in volumetric modulated arc therapy (VMAT) using a dedicated linac. Nevertheless, a harmonization of the planned and delivered doses to the tumor is essential and should not depend on the treatment unit; hence, a change in the method of dose prescription is required.

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For treatment using a robotic-assisted unit, the lack of ITV to generate PTV and the planning on a specific respiratory phase make the dose prescription on D50% or D98% of GTV easy to perform, as suggested by Lacomnerie et al. [3]. Nevertheless, the use of an ITV strategy using a dedicated linac makes this method of dose prescription difficult as GTV is not punctual on the average computed tomography (CT) images. This explains the preference of most centers to prescribe a dose to D95% PTV, as reported by the ESTRO-ACROP consensus [2].

In this study, we developed a method to estimate the doses to the multiple indicators of GTV. We implemented a GTV-based prescription method on D98% GTV using a robotic-assisted unit and a PTV-based prescription method on D95% PTV using a dedicated linac. For validation, the treatment plans of both machines were recalculated and compared using a third-party software that uses a common MC algorithm. An experimental setup on a phantom was used to validate the overall methodologies designed in this study. Finally, standardization of the prescribed doses and the method of prescription of both treatment units were discussed.

2. Materials and methods

2.1. Databases

Data of 32 and 23 patients respectively treated at Cyberknife (Accuray Incorporated, Sunnyvale, CA, USA), hereafter referred to as the robotic-assisted unit, and at VersaHD (Elekta, Crawley, UK), hereafter referred to as the dedicated linac, were collected. At the time of treatment, patients included in this study provided their consent for using their anonymized medical data for research purposes.

The median tumor volumes estimated using robotic-assisted and dedicated linac databases were 7.8 cm$^3$ (0.6 to 52.8 cm$^3$) and 2.2 cm$^3$ (0.5 to 42.8 cm$^3$), respectively. No patient selection was performed based on the tumor position inside the lungs.

Further, 4-dimensional CT (4DCT) images were acquired for all patients at a voltage of 120 kVp and image reconstructions were performed in 10 temporal phases of identical duration (0%, 10%, ..., 90%) with a reconstructed slice thickness of 2 mm. The reconstructed field of view (FOV) generated voxel widths ranged from 0.85 to 1.37 mm.

The database of the robotic-assisted unit included patients who underwent lung optimized treatment (Accuray Inc.) using the two-view modality [5], also called as Xsight Lung (Accuray Inc.); no ITV was generated and PTV was defined as a 5 mm isotropic expansion from GTV. Treatment planning was performed on the expiratory phase (50%) of the 4DCT.

In the dedicated linac database, GTV for each patient was delineated by a radiotherapist in each phase of 4DCT, and ITV was defined as the volume encompassing all GTVs. PTV was generated from ITV with a 5 mm isotropic expansion. Treatment planning was performed on the average CT obtained from 4DCT images.

Statistical comparisons between the GTV and PTV doses of both treatment units were conducted using Mann–Whitney U test.

2.2. Robotic-assisted unit: Prescribing dose on D98% GTV

The Multiplan (Accuray Inc.) treatment planning system (TPS), referred to as the native TPS for the robotic-assisted unit, was used for planning treatments of this unit. This software provides both RayTracing (RT) - type A, MC - type C, algorithms [7]. To ensure homogeneous fluency of PTV, all plans were optimized using the RT algorithm and normalized to D$_{95\%\text{PTV}}$ = 54 Gy, with a maximal dose of 125%–130% of the prescribed dose. This method of prescription (54 Gy on D95% PTV associated with type A algorithm) was selected as a point of departure in this study as it represents the historically used practice in our clinics and is associated with a specific local control. In the second part of the study, the plans were recalculated using the Multiplan MC algorithm with a statistical uncertainty of 2% and a grid spacing equal to the resolution of the CT voxels. Doses D98% and D50% of GTV were collected and averaged. The mean value of D98% GTV of the cohort was rounded and denoted as D98% GTV.

As suggested by Lacomnerie et al. [3], local control for lung SBRT obtained using type A algorithm is very high [8], and switching from algorithm type A to type C should not significantly modify the dose received by the tumor. Hence, a monitor unit (MU) normalization of the individual plans was applied to make the individual D98% GTV equal to D98% GTV. Doses D98%, D95%, D50%, and D2% of GTV and PTV were collected.

This method of dose prescription that used type A algorithm for optimizing the fluence on PTV followed by a recalculation using a type C algorithm and MU normalization to make the D98% GTV of the plan equal to D98% GTV is referred to as method A in this study.

2.3. Dedicated linear accelerator: Prescribing dose on D95% PTV

The Monoac (Elekta, Crawley, UK) TPS with an MC algorithm was used to generate dynamic conformal arc therapy (DCAT) or VMAT plans, depending on the tumor position, for the VersaHD. A grid resolution of 2 mm and a statistical uncertainty of 1% of the treatment plan were used for calculations. All plans were rescaled to obtain D$_{95\%\text{PTV}}$ = 54 Gy in MC on the average CT scan, with a maximal dose ranging from 125% to 150% of the prescribed dose, as recommended by ESTRO-ACROP [2]. This common method of dose prescription on D95% PTV with a type C algorithm is referred to as method B in this study.

Similar to the methods described in the literature [6,9–15], a 4D-sum was created for each patient plan using the MiM Maestro (MiM Software, Cleveland, OH, USA) software. Here, dose plans generated on the average CT were recalculated for individual phases of the 4DCT. Plans were subsequently summed up and weighted by the theoretical time spent in each phase (1/10 of the time for each phase). Doses D98%, D95%, D50%, and D2% [2] of the PTV were collected in the 4D-sum plan.

A deformable registration of the dose maps calculated for individual phases was necessary to assess the GTV doses. The first step involved determining the respiratory phase in which GTV was the closest to its barycentric position, i.e., the midV phase [16]. For each of the nine other respiratory phases, a map of 3D deformations was calculated using the MiM software by registering each GTV contour with the one in the midV phase. For these nine phases, the individual deformations map was applied to the corresponding 3D doses map; 10 doses maps were obtained on the midV phase, summed up, and weighted by the time spent in each phase. Doses D98%, D95%, D50%, and D2% of the GTV were collected for individual patient plans.

2.4. Independent MC algorithm

To exclude the differences linked to the nature of the MC algorithm between Multiplan MC and Monoac, we used a third-party MC module named SureCalc (MiM Software, Cleveland, OH, USA), referred to as the plan double-check software. After the first step of machine modeling, independent MC calculations were performed for our treatment units. The software uses DICOM data of the native treatment plan (CT, RTStruct, RTDose, and RTPlan for Monaco or XML files [report.xml and plan.xml] for Multiplan) to generate a 3D MC dose map. A calculation grid of 2 mm was used associated with a statistical uncertainty of 0.5%.

In the robotic-assisted unit database, 25 patient plans with a prescribed dose of D$_{95\%\text{PTV}}$ = 54 Gy using a type A algorithm in Multiplan were recalculated using the MC algorithm of SureCalc. Doses D98% GTV were collected and compared with those obtained using Multiplan MC; paired Student t-test was used to evaluate the statistical difference between software. MU normalization was individually applied to ensure that D98% GTV of each plan (calculated using SureCalc) corresponds to D98% GTV from the data calculated using Multiplan MC. Individual doses D98%, D50%, and D2% to GTV and PTV were collected and compared with those obtained using Multiplan MC.

In the dedicated linac database, 22 patient plans were investigated;
the initial treatment plan for each patient optimized using Monaco on the average CT and normalized to $D_{95\%\text{PTV}} = 54$ Gy was recalculated using the MC algorithm of SureCalc. Subsequently, plans calculated in each respiratory phase (0 %, 10 %, …, 90 %) using Monaco were recalculated using SureCalc, and the 4D-sum was performed to assess doses to PTV. The deformation maps calculated using data from Monaco were applied to the recalculated data (using SureCalc) to obtain doses of GTV. Doses $D_{98\%\text{GTV}}$, $D_{50\%\text{GTV}}$, and $D_{2\%\text{GTV}}$ to GTV and PTV calculated using the SureCalc and Monaco algorithms were compared.

2.5. Harmonization of dose prescription

The averaged value of the near minimum dose to the tumor ($D_{98\%\text{GTV}}$) between both method A and B was calculated and constituted the trade-off dose. Thus, the prescribed dose of method A and of method B were adjusted to obtain the same value of $D_{98\%\text{GTV}}$ regardless the method.

2.6. Experimental setup

The CIRS Dynamic Thorax Phantom (model 008A) was used for the experimental validation of developed methods. An insert, simulating a tumor and having a sandwiched radiochromic EBT3 film (Ashland Inc., Wayne, NJ, USA), was set in motion following a caudocranial movement with regular motion (cos4 signal model), and 4DCT of this moving phantom was performed similarly (acquisition and reconstruction parameters) as for patients.

For the robotic-assisted unit, a tumor insert of 2 cm diameter was used to ensure a 2-view modality, and a motion amplitude of 6 mm was set. Planning was performed with Multiplan using method A; a dose of $D_{95\%\text{PTV}} = 5.1$ Gy was prescribed using the RT algorithm with a maximal dose of 6.3 Gy, and the plan was delivered to the moving phantom. MC recalculation was performed using both Multiplan MC and SureCalc. Further, 2D maps in the plan of the radiochromic film were extracted and compared with the irradiated film.

For the dedicated linac, a tumor insert of 1 cm diameter was used, and a motion amplitude of 24 mm was applied. The ITV was constructed based on 10 phases of the 4DCT and the PTV was created. A DCAT plan was generated on the average CT with a prescribed dose of $D_{95\%\text{PTV}} = 5.1$ Gy in MC (maximal dose of 6.3 Gy) following method B, and was delivered to the phantom. A recalculation of the initial plan (on average CT) was performed on each respiratory phase with Monaco and SureCalc, and 4D sum was realized. Further, 2D calculated dose maps in the plan of the film were extracted and compared with the dose maps measured using radiochromic film.

DoseLab (Varian Medical Systems, Palo Alto, CA, USA) was used to register the extracted 2D planned dose maps with the irradiated films. Each calculated dose map was registered with the measured dose map using three fiducials. The dose maps registration was then adjusted (2D translations only) to obtain the maximal gamma index values. Obtained shifts (in millimeters) represented the geometric accuracy of the whole process (irradiation plus registration). A tight criteria tolerance of 2 %, 1.5 mm in a local analysis was set with a dose threshold of 10 %.

3. Results

3.1. Method A: determining $D_{98\%\text{GTV}}$

For plans of the robotic-assisted unit database, mean values of $D_{98\%\text{GTV}}$ calculated to GTV and $D_{50\%\text{GTV}}$ GTV with native TPS and double-check software for the database of robotic-assisted unit before MU normalization. The p-value is calculated using a paired Student’s t-test.

| Indicator  | Native TPS | Double check software | p-value |
|------------|------------|------------------------|---------|
|            | Mean ± SD  | Median [Range] (Gy)    |         |
| $D_{98\%\text{GTV}}$ | 49.2 ± 3.6 | 49.5 [38.4-55.3]       | 0.4     |
| $D_{50\%\text{GTV}}$ | 55.1 ± 3.5 | 55.3 [45.2-62.7]       | 0.4     |

Fig. 1. Dose differences (%) to doses indicators calculated for: (Upper left): method A (data from the robotic-assisted unit) for GTV indicators between the plan double check calculations and native TPS, (Upper right): method A (data from the robotic assisted unit) for PTV indicators between the plan double check calculations and native TPS, (Lower left): method B (data from the dedicated linac) for GTV indicators between the plan double check calculations and native TPS, (Lower right): method B (data from the dedicated linac) for PTV indicators between the plan double check calculations and native TPS.
and D50% GTV calculated using native TPS and double-check software are presented in Table 1. First, no significant differences were observed between software for both the dose indicators. The median dose to GTV (D50% GTV) was close to the value 54 Gy, which was prescribed with the type A algorithm on D95% PTV. The mean dose to D98% GTV, ranging between 49.2 Gy and 49.4 Gy depending on the software, was rounded off to D98% GTV = 49.5 Gy (3 × 16.5 Gy). Then, with method A, the MU normalization to have individual D98% GTV = 3 × 16.5 Gy corresponded to a normalization factor of 1.01 ± 0.08 (range, 0.89–1.29).

3.2. Individual plan double check calculations

In Fig. 1, relative differences in GTV and PTV doses between the double-check calculation software and respective native TPS for methods A and B were evaluated as a function of GTV (cm³) by considering three dose indicators of a volume (D98%, D50%, and D2%).

Method A applied on the database of the robotic-assisted unit showed discrepancies < 2.5 % between the double-check software and native TPS for both GTV and PTV. Dose differences did not seem to be dependent on GTV size as they fluctuated regardless of GTV.

Method B applied on the database of the dedicated linac showed larger discrepancies between the two software for both GTV and PTV and reached up to 7.4 % and 10.4 % for the indicator D98% GTV and D98% PTV, respectively. However, these individual dose differences tended to decrease for larger GTV.

3.3. Method A and B: Dose evaluation for GTV and PTV

Dose distributions for the indicators of GTV D98%, D95%, D50%, and D2% calculated using their respective native TPS are presented in a boxplot format in Fig. 2 for method A (with the robotic-assisted unit database) and for method B (with the dedicated linac database). For method A, the dose normalization of the plans implied no disparity for the indicator D98% GTV at the value 49.5 Gy, but the spread of the distribution, based on the IQR, tended to increase for other indicators especially for higher doses (D2% GTV). However, no outlier was observed for method A, whereas method B had a smaller standard deviation but seemed to generate more outliers regardless of the dose indicator. Method B generated higher doses, and large dose differences were observed between the two methods for all dose indicators. The averaged dose difference between method B and method A was 10.5 Gy for D98% GTV (p < 0.001) and 7.2 Gy for D50% GTV (p < 0.001). The double-check software showed an averaged dose difference between these two methods of 10.2 Gy for D98% GTV (p < 0.001) and 7.3 Gy for D50% GTV (p < 0.001).

In Fig. 3, doses to different indicators of PTV calculated using their respective TPS are presented for both methods A and B. We noticed that method B tended to generate more outliers compared with method A, except for the indicator D50% PTV. A significant difference between both methods of 11.0 Gy (p < 0.001) and 10.9 Gy (p < 0.001) was observed for the indicators D98% PTV and D95% PTV, respectively. The double-check software confirmed these results with a dose difference between the two methods of 11.7 Gy for both D98% PTV and D95% PTV (p < 0.001 and p < 0.001, respectively).

3.4. Harmonization of dose prescription

From Fig. 2 doses to D98% GTV were 49.5 ± 0.0 Gy and 60.0 ± 1.7 Gy for methods A and B, respectively, calculated using their native TPS. In Fig. 3, doses to D95% PTV were 42.6 ± 1.9 Gy and 53.5 ± 2.0 Gy for methods A and B, respectively, calculated using their native TPS.

A trade-off value of the near-minimum dose delivered to the tumor corresponded to D98% GTV = 55 Gy (3 × 18.3 Gy). This required a dose increase of 11.0 % for method A (robotic-assisted unit) and a dose drop of 8.3 % for method B (dedicated linac). A recapitulative scheme is presented in section supplementary material. Finally, to obtain the same dose value D98% GTV for both methods, method A consisted of prescribing 3 × 20 Gy with a type A algorithm to D95% PTV, in recalculating the plan with a MC algorithm and in performing a small MU normalization to match D98% GTV = 55 Gy. Method B consisted of prescribing 3 × 16.5 Gy with a MC algorithm to D95% PTV.

3.5. Experimental results

The gamma index values of both experiments are summarized in Table 2. Gamma indexes ≥ 97.8 % were obtained between the dose maps measured on radiographic films and predicted dose maps calculated by native TPS of robotic-assisted unit, native TPS of dedicated linac, and plan double-check software. The geometric uncertainties of the overall process were inferior to 1 mm for both treatment units. Minor differences were observed between the calculation made by the native TPS of
each treatment unit and the plan double-check software.

4. Discussion

In this study, two dose prescription methods for two different treatment units were evaluated for the treatment of NSCLC by SBRT. As dose calculations were performed on different TPS, the use of a plan double-check software was interesting because of its ability to recalculate plans with an MC algorithm regardless of the treatment unit and of the planning software. The double-check calculations showed a few large discrepancies for dose estimators to GTV and PTV in some plans of the method B, especially for small GTV. In fact, a small GTV constituted a parameter of complexity for doses calculation as the tumor volume was represented by a small number of voxels, and a dose difference in few voxels may induce large variations in the calculations of D98% GTV between the two types of software. Nonetheless, on average for all plans for method A or B no clinically relevant difference was observed between the respective native TPS and plan double-check software. Thus, using plan double-check software allowed us to validate the mean values of different doses indicators to GTV and PTV obtained in this study.

Figs. 2 and 3 showed that method A, with the step of dose normalization on GTV, allows to obtain homogenous doses to D98% GTV, D50% GTV, and D2% GTV. This is consistent with the results of Leung et al. [17] who reported a statistically significant reduction of interpatient variability in GTV doses when dose prescription was performed on the indicator D50% GTV rather than PTV. We chose prescription to D98% GTV (rather than D50% GTV) to provide physicians with an opportunity to visually evaluate on a TPS the coverage of GTV at 98 % of its volume with the prescribed dose level. Even though method A for dose prescription in lung SBRT is considered as more robust in the literature [3,4,17,18], its implementation with an ITV strategy is not straightforward and must be based on a local evaluation by the team and on clinical outcomes in prospective studies, as previously suggested [22,23].

In conclusion, we developed a method to deliver similar near-minimum doses to the tumor (D98% GTV) of approximately 55 Gy (3 × 18.3 Gy) using a GTV-based prescription on a robotic-assisted unit (method A) and a PTV-based prescription on a dedicated linac (method B). Thus, in this study we provided a standardization of the prescribed dose for SBRT treatments of NSCLC on two types of treatment units associated with different methods of dose prescription.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.phro.2022.09.007.

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