Original Article

Statistic and dosimetric criteria to assess the shift of the prescribed dose for lung radiotherapy plans when integrating point kernel models in medical physics: are we ready?

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Background: To apply the statistical bootstrap analysis and dosimetric criteria's to assess the change of prescribed dose (PD) for lung cancer to maintain the same clinical results when using new generations of dose calculation algorithms.

Methods: Nine lung cancer cases were studied. For each patient, three treatment plans were generated using exactly the same beams arrangements. In plan 1, the dose was calculated using pencil beam convolution (PBC) algorithm turning on heterogeneity correction with modified batho (PBC-MB). In plan 2, the dose was calculated using anisotropic analytical algorithm (AAA) and the same PD, as plan 1. In plan 3, the dose was calculated using AAA with monitor units (MUs) obtained from PBC-MB, as input. The dosimetric criteria's include MUs, delivered dose at isocentre (Diso) and calculated dose to 95% of the target volume (D95). The bootstrap method was used to assess the significance of the dose differences and to accurately estimate the 95% confidence interval (95% CI). Wilcoxon and Spearman's rank tests were used to calculate P values and the correlation coefficient (ρ).

Results: Statistically significant for dose difference was found using point kernel model. A good correlation was observed between both algorithms types, with $\rho>0.9$. Using AAA instead of PBC-MB, an adjustment of the PD in the isocentre is suggested.

Conclusions: For a given set of patients, we assessed the need to readjust the PD for lung cancer using dosimetric indices and bootstrap statistical method. Thus, if the goal is to keep on with the same clinical results, the PD for lung tumors has to be adjusted with AAA. According to our simulation we suggest to readjust the PD by 5% and an optimization for beam arrangements to better protect the organs at risks (OARs).

Keywords: Pencil kernel; point kernel; anisotropic analytical algorithm (AAA); prescribed dose (PD); bootstrap

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Introduction

The dose calculation algorithms integrated in a radiotherapy Treatment Planning System (TPS) compute the medical prescribed dose (PD) into a representation of the delivered dose (DD), of the same expected value in gray, to the patient, itself translated in monitor units (MUs) actually delivered by the radiotherapy machine. This is a

fundamental fiducial chain between the treatment desired by the medical oncologist and the physical dose, and clinical effect, truly obtained in the patient. As everyone knows the relation between the PD and the DD is not yet exact in all anatomical situations or with all calculation algorithms. Since the generalization of predictive and personalized dosimetry with 2 and 3D dose distributions and dose volume histograms (DVH) one could easily forget this caveat and imagine to see the truth on treatment plan. This is almost right for density rather homogeneous anatomic regions as brain, pelvis, abdomen, etc. but it is still a search for density very heterogeneous regions as chest because of the very low density of lungs. The progress toward always better calculation algorithms is not linear. Impressive progresses have been made considering heterogeneities but with low consideration regarding the real physical processes of dose deposition, and more recently increasing consideration is given to dose deposition mechanism's going closer and closer to Monte Carlo simulation results, taken as reference. Most of the Radiation Oncology departments had, in the recent years, to go through successive changes of dose calculation algorithms according to the evolution of those software's. In this paper, the evolution of the relation between the PD and the DD is examined through the most current situation of change from pencil beam convolution with modified batho (PBC-MB) to anisotropic analytical algorithm (AAA). The point of view is the quantification of the altered PD to consider, when one wishes to keep on with the same physical DD or clinical results, when implementing such changes (1-3). This concern should, of course be extended to organs at risk (OARs), or integrate dose escalation, but this is out of the scope of this report which focus on the methodological issues.

Methods

Dose calculation algorithms

The most commonly dose calculation models for photon beam therapy, as pencil kernel and point kernel, were used in this study. The dose calculations were performed using PBC-MB as pencil kernel model and AAA as point kernel model. Both algorithms were integrated in Eclipse® TPS (Version 8.1; Varian Medical Systems, Palo Alto, CA, USA). The pencil beam convolution (PBC) computes the dose to the patient as the superposition of the total energy released per mass unit within an energy deposition kernel. The kernel represents the spread of energy from the primary photon interaction site throughout the volume (4-7). For inhomogeneity correction, PBC-MB method first calculates a relative dose distribution within a water-equivalent medium, and then adds an inhomogeneity correction factor. In the AAA all energy from a photon interaction is deposited either in the forward beam direction or along one of 16 lateral transport lines, all located in the plane perpendicular to the incident beam direction. AAA presents more accurate algorithm as compared to pencil kernel algorithm (8-10).

Clinical cases and treatment planning

Nine lung cancer cases have been included in this study. Radiation oncologists delineated the anatomic borders of planning target volume (PTV) and OARs. The treatment plans were 3D conformal plans using multi-leaf collimators (MLC). The average target volume was 394.0±194.0 mL, treated with a mean PD of 58.8 Gy (range, 50.8–66 Gy) and n=34 beams. For each patient, three treatments plans were generated using exactly the same beams arrangements (11,12). In plan 1, the dose was calculated using PBC-MB. In plan 2, the dose was calculated using AAA and the same PD as plan 1. In plan 3, the dose was calculated using AAA with MUs obtained from PBC-MB as input. The plan 3, having the MUs from plan 1, shows a display of the dose distributions of the former treatments, taken as references, recalculated with the new algorithm. In all plans, the PD is considered at a single reference point at the isocentre. The reference treatment plan was generated according to the clinical experience of the department and the ICRU recommendations (13,14). The validation of a treatment plan requires that 95% of PTV should be covered by 100% of the PD and the maximum dose within the PTV was under 107% of PD. For OARs, the dose constraints were respected. In our point of view, the choice of plan 1, with pencil kernel model, as the reference was justified by the clinical experience accumulated over several years with the corresponding algorithms.

Dosimetric criteria's

The MUs characterize the irradiation time from linac and the dose criteria's to validate a treatment plan are based on DVH parameters. Thus, the three criteria were used:

DD: the MUs from the plan 1 and 2 were compared. Then, the delivered dose at isocentre (Diso) recalculated in plan 3 was compared with the initial PD in plans 1 and 2.

DVH indices: for each PTV the calculated dose to 95%

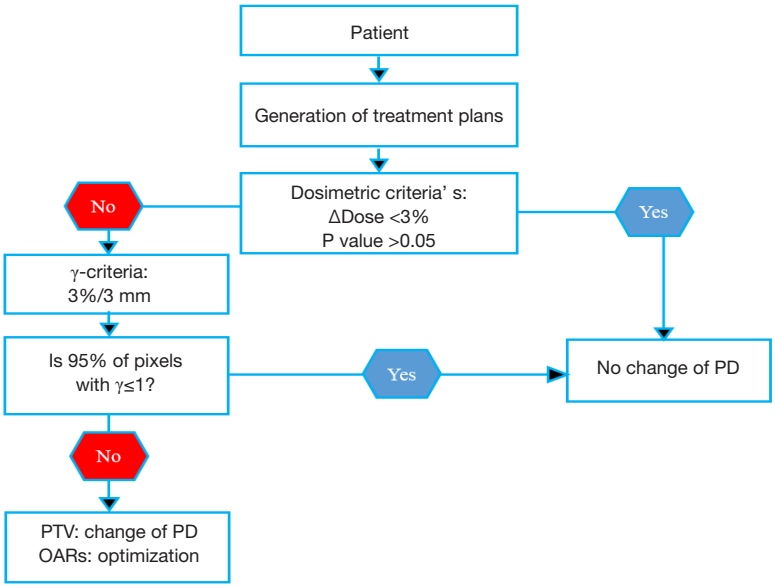

Figure 1 Suggested medical decisions concerning the modification of PD when moving from reference algorithm, pencil kernel, to point kernel. PD, prescribed dose; PTV, planning target volume; OARs, organs at risk.

of the target volume (D95) from all plans were compared.

Gamma analysis

The γ-index combines two criteria including the dose difference in percentage (ΔDose) and the distance-to-agreement (DTA) in millimeters. An ellipse is used to determine the acceptable region. The γ-value ≤1 represents fulfillment of the criteria (15). Our goal was to quantify the magnitude of the impact of dose calculation models on "real" DD. The Dicom images including dose distribution from pencil kernel and point kernel models, for each patient were exported to RIT-113® (Dosimetry System Version 5.2, Radiological Imaging Technology, Inc., CO, USA). The pixels with γ≤1 present the pixels having the same dose distribution. The pixels with γ>1 show under/overestimated dose associated with new dose calculation model compared to reference one. Using 3%/3 mm, the 95% of pixels should have γ≤1.

Statistical analysis

The bootstrap simulation method was used to estimate the minimum number of fields "beams" to observe a significant difference between algorithm models. Then, the data resulting from the simulation was used to estimate the 95% of confidence interval (95% CI). This consisted in taking 1,000 random samples of size "n", with n=5 to n=34. For each sample size, P value was computed using Wilcoxon signed-rank test (16). The dose difference is considered significant, if P<0.05. The statistical correlation between calculated doses was evaluated using Spearman's correlation coefficient (ρ).

Medical decisions

The objective of the comparison between pencil kernel and point kernel is to check if the PD should be readjusted. We considered that if there is a statistically significant, P<0.05, for dosimetric indices, the PD should be readjusted. The significant differences reflect with 95% of confidence existing differences between algorithms. To make a medical decision, three successive evaluations were carried out using MUs, Diso and D95, as mentioned above. *Figure 1* shows which medical decision could be considered regarding the alteration of the PD when moving from reference algorithm to new one.

Results

Comparison of DD

MUs: the AAA in plan 2 calculated significantly more MUs

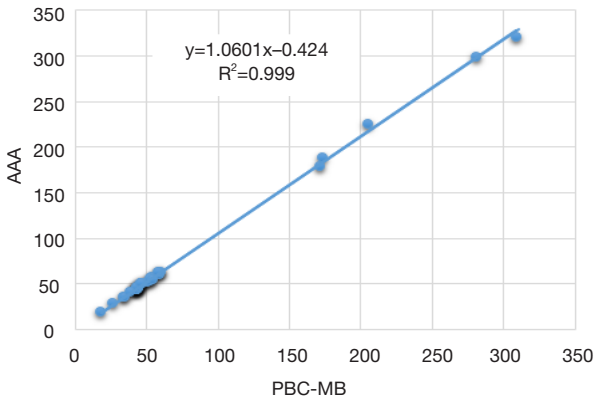

Figure 2 correlation between the MUs from pencil kernel compared with point kernel. MUs, monitor units; PBC-MB, pencil beam convolution with modified batho; AAA, anisotropic analytical algorithm.

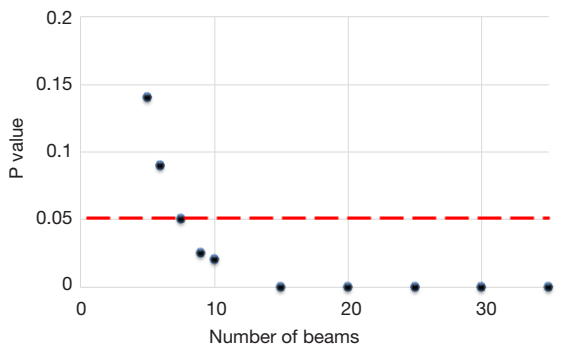

Figure 3 P value estimated by bootstrap simulation, indicating the average P value for each sample-size going from n=5 to n=34. The red dashed line corresponds to a significance threshold of 0.05.

than the PBC-MB in plan 1 using the same PD. The 95% CI for ΔMUs evaluated with bootstrap simulation was (3.9; 5.5). The Wilcoxon test showed a significant difference, with P<0.001 and the data showed a strong correlation, with ρ>0.9. *Figure 2* shows the correlation between the MUs from pencil kernel with point kernel. *Figure 3* shows the computed average P value for each sample size, going from n=5 to n=34. It can be seen in *Figure 3* that eight beams would have been sufficient to observe a significant difference between AAA versus PBC-MB.

Diso: using the same MUs form PBC-MB algorithm, the AAA in plan 3 calculated significantly less dose than initially prescribed in plans 1 and 2, as shown in *Figure 4*, with P=0.03 and ρ=0.99. The 95% CI for ΔDiso evaluated

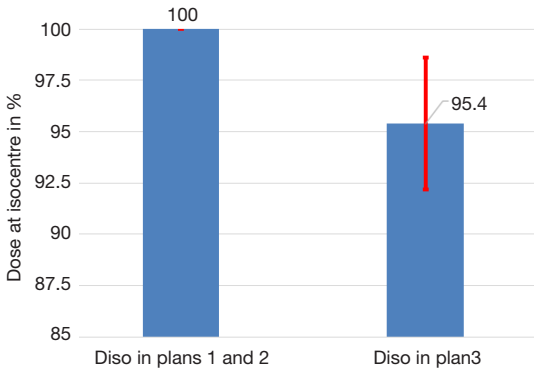

Figure 4 The dose at isocentre point "Diso" normalized to 100% from PBC-MB compared with AAA. Diso, delivered dose at isocentre; AAA, anisotropic analytical algorithm; PBC-MB, pencil beam convolution with modified batho.

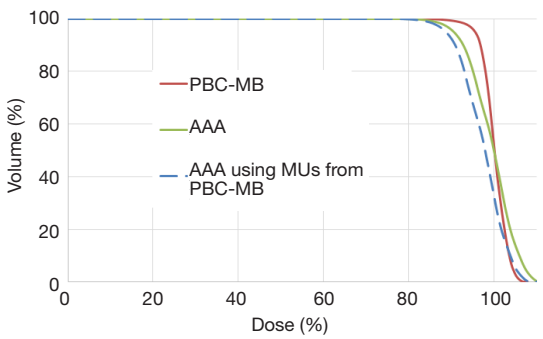

Figure 5 Cumulative DVH from plans 1, 2 and 3 when moving from PBC-MB to AAA. The 100% of PD was normalized to 100% at isocentre for all plans. The dose in plans 1 and 2 were calculated using the same beam arrangements and PD. The dose in plan 3 was recalculated using AAA with the same MUs from PBC-MB. The D95 were 96%, 92% and 90%, respectively, using plans 1, 2 and 3. DVH, dose volume histograms; PBC-MB, pencil beam convolution with modified batho; AAA, anisotropic analytical algorithm; MUs, monitor units; PD, prescribed dose.

by bootstrap simulation was (3.3; 5.8).

Comparison of calculated dose to 95% of PTV

The AAA in plans 2 and 3 calculated significantly less D95% than the PBC-MB in plan 1. The 95% CI for ΔD95 was (10.0; 15.0), with P<0.01 and ρ=0.9. *Figure 5* shows the cumulative DVH from all plans. It can be seen that AAA in plans 2 and 3 calculated significantly less D95 for the PTV.

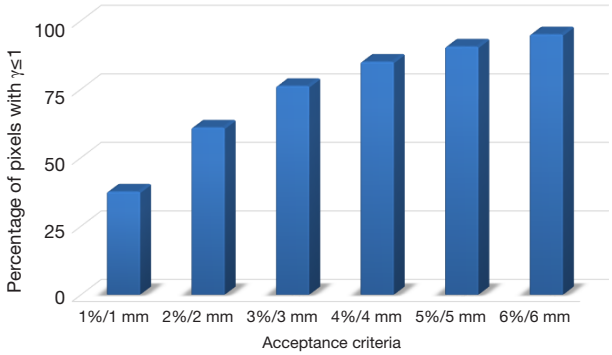

Figure 6 The percentage of pixels having γ≤1, by varying dose-difference and DTA criteria. It can be seen that 60% and 74% of pixels have γ≤1 using 2%/2 mm and 3%/3 mm, respectively. The tolerance 95% of pixels with γ≤1 was satisfied using 6%/6 mm.

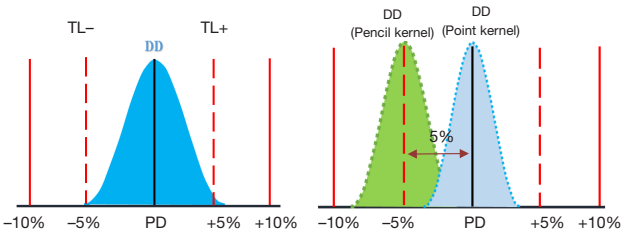

Figure 7 An illustration for the recommended DD with TL = ±5%, on left panel, and an estimated DD from pencil beam and point kernel models on right panel. It can be seen that an overestimation of "real" DD about 5% from pencil beam model exists, compared with the point kernel model. DD, delivered dose; TL, tolerance limit.

Gamma analysis

The tolerance limit (TL), 95% of pixels having γ≤1, is not respected at all using routinely γ criteria with 2%/2 mm or 3%/3 mm. However, to satisfy the γ tolerance, at least 6%/6 mm is needed. *Figure 6* shows the percentage of pixels having γ≤1, by varying dose-difference and DTA criteria. The significant difference for dose distribution is due to the wide range of electron transport in the lung. The point kernel algorithms are more accurate than pencil kernel algorithms due to their ability to approximately model the electron transport.

Discussion

There are numerous studies recommending integrating carefully, into clinical use, the new dose calculation algorithms (17-19). Recently, Chaikh *et al*. [2014] reported that the change of dose calculation algorithm might be associated with the adjustment of the dose prescription for clinical purpose (3). In this paper we compared three parameters using two calculation algorithms. Our comparisons were based on 34 fields. The comparison of MUs, as first step, made these changes obvious. For the same PD, the MUs were increased when moving from PBC-MB to AAA. The differences in MUs were influenced by the field size, the anatomical structures surrounding the lung, the beam incidence and orientation. A statistical evaluation based on Wilcoxon's test showed a significant difference, also confirmed with the 95% CI of the existing differences. Consequently, keeping the same PD, the risk due to the change from PBC-MB to AAA was an increased dose to the target. In addition, the bootstrap simulation indicated that the significant differences between dose calculation algorithms could be ascertained with as little as n=8 beams. The results obtained from MUs were confirmed by the comparison of dosimetric indices and 2D gamma analysis, with $P<0.05$. When the dose distribution was calculated by AAA, using the same PD, the dose difference was more than 3%/3 mm for all cases. Considering the results from 2D gamma, the major of pixel values don't meet the criteria 95% of pixels with γ≤1 using routinely recommendation 2%/2 mm or 3%/3 mm (20,21). The results confirm that an optimization of beam weights and arrangement should be performed, for heterogeneity correction with point kernel model, to protect the OARs in thorax region including spinal cord, esophagus, heart and healthy lungs. All these organs were affected by turning-on the heterogeneity correction with AAA, since the secondary electrons go more through the organs due to the lower density of lungs.

Considering AAA is to be a more accurate algorithm, the comparison between the AAA and PBC-MB provides an indication of the dose-difference for real DD for a decade using PBC-MB. Considering, a satisfaction outcomes with the former algorithm, our results suggest a reduction of 5% for Diso to respect the dose conformity to PTV using point kernel model. *Figure* 7 shows an illustration for the recommended DD with a TL and the real DD from pencil beam model and point kernel model. The data used to determine the DD were obtained from bootstrap simulation method "in-silico" from treatment plans using both dose calculation models. The TL =±5%, used in the illustration, for dose deviations were suggested in ICRU reports (13,14).

However, the real clinical outcome, such as tumor control probability and normal tissue complication probability as endpoint, should be used to determine the DD ± TL. Ideally, more appropriate radiobiological models with clinical parameters, real clinical trials outcomes and clinical experience are needed to better estimate the radiotherapy outcomes.

Conclusions

This paper shows that the alterations of dose estimations are quite important when changing the calculation algorithm in radiotherapy. It is at least of the order of magnitude of dosimetric cumulated uncertainties considered as inacceptable (>5%). Therefore, these alterations need to be known and taken into account in the process of quality assurance in radiation oncology. This alteration could be an increment or a reduction of the PD according to the type of the new algorithm which is substituted to the former one. Actually, in our virtual course to more and more accuracy, hopefully toped some days by the MC simulation, the changes are not all going in the same direction. This could be a source of misunderstanding between the radiation oncologists and their associated medical physicists. Moreover, many parameters are influencing these results and it is difficult to imagine finding the truth all done in the literature. Ideally, each radiation oncology department should be able to assess this question and it is interesting to see that rather simple tools are existing and are powerful enough to allow making a valuable study with a small set of patients, any department could find among its own workflow.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: We declare that the article does not require a Statement of Ethics, since all the clinical material was anonymized CT-scans images used for dosimetric repeated assay's at a remote time from the real treatment of the patients as mentioned in section (2.2). Absolutely no information concerning the patients, themselves, were used, so no consent were necessary. The study has been carried out in the University Hospital of Grenoble, France.

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