Original Article

Assessing the shift of radiobiological metrics in lung radiotherapy plans using 2D gamma index

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Background: The purpose of this work is to investigate the 2D gamma (γ) maps to illustrate the change of radiobiological outcomes for lung radiotherapy plans and evaluate the correlation between tumor control probability (TCP), normal tissue complication probability (NTCP) with γ passing rates (γ-rates).

Methods: Nine patients with lung cancer were used. The doses were calculated using Modified Batho method integrated with pencil beam convolution (MB-PBC) and anisotropic analytical algorithm (AAA) using the same beam arrangements and prescription dose. The TCP and NTCP were estimated, respectively, using equivalent uniform dose (EUD) model and Lyman-Kutcher-Burman (LKB) model. The correlation between ΔTCP or ΔNTCP with γ-rates, from 2%/2 and 3%/3 mm, were tested to explore the best correlation predicting the relevant γ criteria using Spearman's rank test (ρ). Wilcoxon paired test was used to calculate P value.

Results: TCP value was significantly lower in the recalculated AAA plans as compared to MB plans. However, AAA predicted more NTCP on lung pneumonitis according to the LKB model and using relevant radiobiological parameters (n, m and TD50) for MB-PBC and AAA, with P=0.03. The data showed a weak correlation between radiobiological metrics with γ-rates or γ-mean, $\rho<0.3$.

Conclusions: AAA and MB yield different TCP values as well as NTCP for lung pneumonitis based on the LKB model parameters. Therefore, 2D γ-maps, generated with 2%/2 or 3%/3 mm, could illustrate visual information about the radiobiological changes. The information is useful to evaluate the clinical outcome of a radiotherapy treatment and to approve the treatment plan of the patient if the dose constraints are respected. On the other hand, the γ-maps tool can be used as quality assurance (QA) process to check the predicted TCP and NTCP from radiobiological models.

Keywords: Tumor control probability (TCP); normal tissue complication probability (NTCP); radiotherapy; gamma

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Introduction

Modern radiotherapy treatment planning systems (TPS) and irradiation techniques provide an increasing number of competing treatment plans, showing more accurate dose distributions in the patient. The clinical data sets for radiotherapy outcomes are also relevant and can be used to compare the radiobiological results from different plans. In recent years, the commercially available TPS have a mathematical algorithms and dose response models to objectively compare the treatment plans and make a clinical

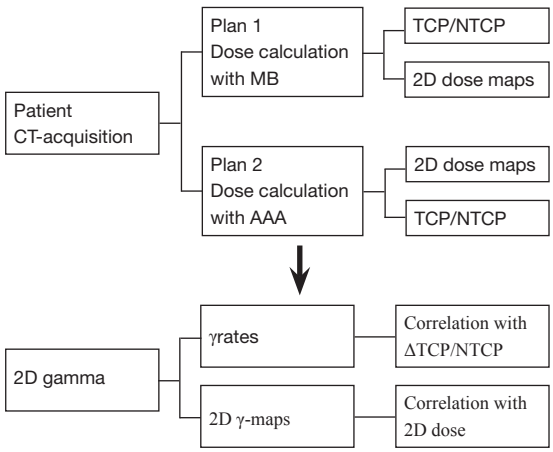

Figure 1 Flowchart from CT acquisition to statistical analysis. CT, computed tomography; TCP, tumor control probability; NTCP, normal tissue complication probability; MB, Modified Batho; AAA, anisotropic analytical algorithm.

decision (1-8). They were able to compute radiobiological metrics including tumor control probability (TCP) and normal tissue complication probability (NTCP). The decision to select a particular plan for treatment is generally made by a radiation oncologist or a medical physicist based on better values of TCP and lower toxicity predicted by NTCP models. However, when moving from former algorithm to the new generations without any clinical data, it would be difficult to select the better estimated radiobiological parameters models. The purpose of this paper is to assess the shift of TCP/NTCP radiobiological outcomes in radiotherapy plans using 2D gamma (γ) topographic. Then, to test the correlation between γ passing rates (γ-rates) or (γ-mean) with ΔTCP/ΔNTCP in order to select the more clinically relevant γ to compare radiotherapy plans.

Methods

The clinical cases and treatment planning

This study is based on nine patients with lung cancer. The computed tomography (CT-scans) images of each patient were loaded into Eclipse® TPS (Varian Medical Systems, Palo Alto, CA, USA). Clinicians delineated the anatomic borders of target volumes (TV) and organs at risks (OAR) including healthy lung and spinal cord, etc. Prescription dose ranged from 50 to 66 Gy in 2 Gy per fraction. Two treatment plans were generated for each patient using the same beam's arrangement making a change of dose distribution due to lung density correction. The dose in plan 1 was calculated using Modified Batho's integrated with pencil beam convolution (MB-PBC) algorithm and the dose in plan 2 was recalculated with anisotropic analytical algorithm (AAA) (9-12). *Figure 1* shows a flowchart from the CT acquisition to the statistical analysis to evaluate the correlation between radiobiological metrics and γ results (*Figure 1*). 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 clinical cases and treatment planning. Absolutely no information concerning the patients, themself, were used, so no consent were necessary. The study has been carried out in the University Hospital of Grenoble, France.

The 2D gamma passing rates

The γ index combines two criteria including the dose difference (ΔDose) in percentage and the distance-to-agreement (DTA) in millimeters (mm). An ellipse is used to determine the acceptable region, and γ≤1 represents fulfillment of the criteria (13-15). Our goal, firstly was to determine the volume ratio receiving the same irradiation, in terms of γ, including the TV and OAR. Secondly, to test if 2D γ-maps illustrate the change of TCP/NTCP. The DICOM images for each patient were exported from TPS to RIT-113® (Dosimetry System Version 5.2, Radiological Imaging Technology, Inc., CO) including the dose distributions. The dimensions were 20×20 cm² with a resolution of 0.39 mm. The results were displayed using 2D γ topography (γ-maps). The γ-maps show the pixels with γ values greater than unity that were outside of tolerance range. To obtain γ values and generate γ-maps. The pixels with γ≤1 present the pixels from the tested plan and reference plan having the same dose distribution. The pixels with γ>1 show either an under- or overestimated dosage associated with plan 2 compared to plan 1. In order to discriminate between an over- and an under-estimated dose, a color code was attributed to the ΔDose. The difference in percentage was calculated as:

$$\Delta\text{Dose}\,(\%) = (\text{Dplan2} - \text{Dplan1}) \times 100/\text{Dplan2} \quad [1]$$

The gamma criteria 2%/2 and 3%/3 mm were used. The

percentage of pixels (PP) having a dose out the tolerance (±2% or ±3%), were separated into fractions:

$$PP = (PD^{+}) + (PD^{-}) \quad [2]$$

where PD^{+} is the pixels exceeding dose tolerance (ΔDose >+2%) presenting the pixels having more dose, Dplan2 > Dplan1. PD^{-} is the pixels exceeding dose tolerance (ΔDose <−2%) presenting the pixels having lower dose, Dplan2 < Dplan1. Using the γ criteria 2%/3 or 3%/3 mm, we considered that the reference and tested plans were similar, if 95% of pixels had γ≤1.

Radiobiological model and outcomes assessment

TCP: the equivalent uniform dose (EUD) model proposed by Niemierko 1997 was used to estimate TCP (16-18):

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma 50}} \quad [3]$$

EUD was calculated as:

$$EUD = \left(\sum_i v_i D_i^a\right)^{1/a} \quad [4]$$

where "*vi*" is the fractional organ volume receiving a dose "*Di*" and "*a*" is a tissue specific parameter that describes the volume effect and γ_{50} describes the slope of the dose-response curve. TCD_{50} is the dose to control 50% of the tumors. The following input parameters, for the TCP model for lung tumors, were used: TCD_{50} =51.24, γ_{50} =0.83 and a=−10 (19).

NTCP: the LKB model was used for estimating NTCP on lung pneumonitis (20-23):

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}dx} \quad [5]$$

$$t = \frac{(EUD - TD50)}{m.TD50} \quad [6]$$

The parameter "m" represents the slope of the sigmoid dose response curve and "TD50" is the dose for a complication rate of 50%. EUD is the equivalent uniform dose and is calculated as:

$$Deff = \sum_i (viEQD2_i^{1/n})^n \quad [7]$$

where "*vi*" is the partial volume, "n" is the volume effects parameter. "EQD2" is the equivalent dose given in 2 Gy fractions. In the present study the radiobiological parameters for lung pneumonitis from Emma were used for PBC and AAA (24). For PBC, the parameters were taken as: n=0.99, m=0.37, TD_{50} =30.78 Gy. For AAA, the parameters were: n=0.99, m=0.374, and TD_{50} =29.19 Gy. In addition, we used α/β=3.0 Gy for normal lung tissue.

The statistical analysis

Bootstrap simulation method with 1,000 random samplings was used to calculate the 95% confidence interval (95% CI) for TCP and NTCP. The statistical significance difference for TCP/NTCP from plans 1 and plans 2 was assessed using the Wilcoxon signed-rank test. The significant difference is considered when P<0.05 (25). In addition, the agreement between γ-rates with ΔTCP or ΔNTCP was statistically assessed using the correlation coefficient (ρ) from Spearman's rank test.

Results

The 2D dose distribution

Figure 2 shows a 2D dose maps plotted in the axial plane using CT-scan corresponding to treatment for one patient. It can be seen in *Figure 2* that the 95% isodose does not cover properly the target in plan 2, but they were extended more in the lateral direction and encompasses more normal lung tissue (*Figure 2*).

The gamma passing rates

Figure 3 shows the results of γ-rates indicating the total pixels with γ>1, under and over dosed pixels for 2%/2 and 3%/3. It can be seen on *Figure 3* that both methods, PBC-MB and AAA, yield much difference using 2%/2 or 3%/3 mm (*Figure 3*). *Figure 4* shows a sample of a 2D γ-maps in the axial views illustrating the γ values and dose differences. The 2D γ-maps were calculated using DICOM images from plan 1 and plan 2 including tumor and organs at risks. The red and blue coloring indicate that γ>1 and identifying PD^{+} or PD^{-} (*Figure 4*).

Radiobiological metrics

Figure 5 shows the results of bootstrap distributions based on 1,000 replications for TCP and NTCP with 95% CI from PBC-MB or AAA. It can be seen in *Figure 5* that MB-PBC in plan 1 predicted more TCP with lower NTCP, P=0.03 (*Figure 5*).

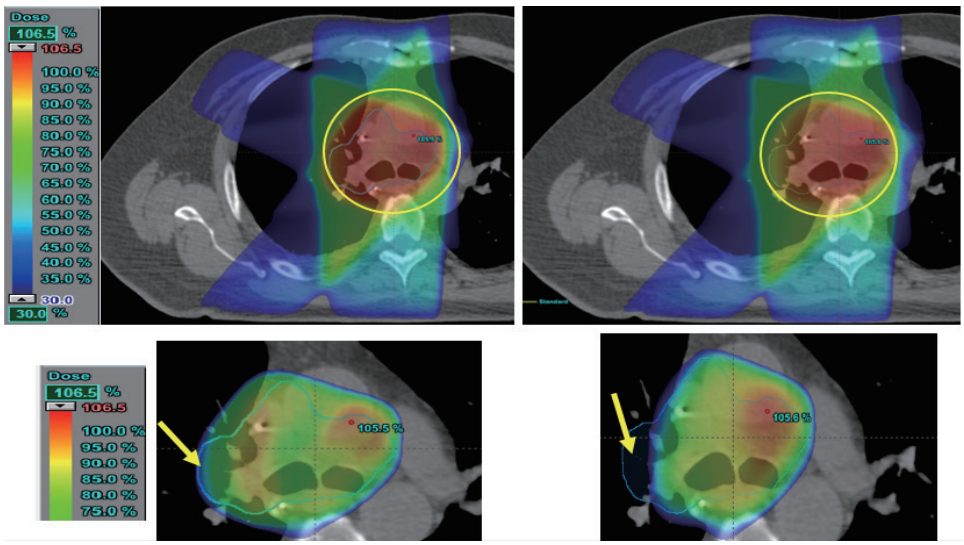

Figure 2 Dose maps in 2D plotted in the axial plane using CT-scan corresponding to treatment for one patient. Left images are MB prediction and right images the AAA one showing obvious shift for dose distribution. CT, computed tomography; MB, Modified Batho; AAA, anisotropic analytical algorithm.

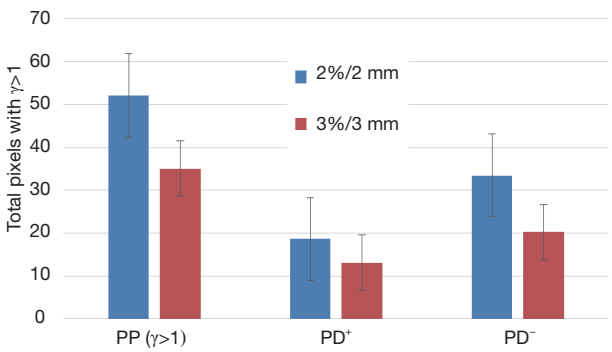

Figure 3 Results of 2D γ passing rates indicating the total pixels with γ>1, under dosed pixels (PD^-) and overdosed pixels (PD^+) using 2%/2 and 3%/3 mm criteria.

Correlation and sensitivity analysis

We observed a weak correlation between γ-rates and ΔTCP or ΔNTCP for 2%/2 or 3%/3 mm. A similar weak correlation between γ-mean and radiobiological metrics was observed, with $\rho<0.3$.

Discussion

Numerous studies have evaluated the correlation between γ-rates and dose volume histogram (DVH) metrics per organ (26-28). They reported a poor correlation between γ-rates and DVH data. Recent studies applied the radiobiological metrics on quality assurance (QA) process with intensity modulated radiation therapy techniques (29-31). They reported the potential useful of biological metrics in-patient specific QA for evaluating the clinical outcome of a radiotherapy treatment. This paper highlights the discrepancies in estimating TCP/NTCP based on EUD and LKB models, respectively, for the same patient and prescribed dose using MB-PBC versus AAA. In our study firstly, we observed an overestimation of TCP by MB-PBC than AAA. On the other hand, a remarkable and significant discrepancy in estimating NTCP was observed confirming the results of several other studies (32-34). Secondly, γ-maps confirmed the observed results from CT imaging showing dose distribution. For example, it can be seen in *Figure 3* that the 95% isodose does not cover the target at all in plan 2, but they were more extended in lateral direction in normal tissues. This will affect the target coverage and TCP values as well as NTCP. The observed results with 2D gamma maps confirm the results from 2D dose maps with CT-scans and alter the change of TCP/NTCP. Furthermore, the tolerance 95% of pixels with $\gamma\leq1$ is not respected, predicting a significant difference between plan 1 and plan 2. The changes of dose distribution in the target and OAR should be taken into

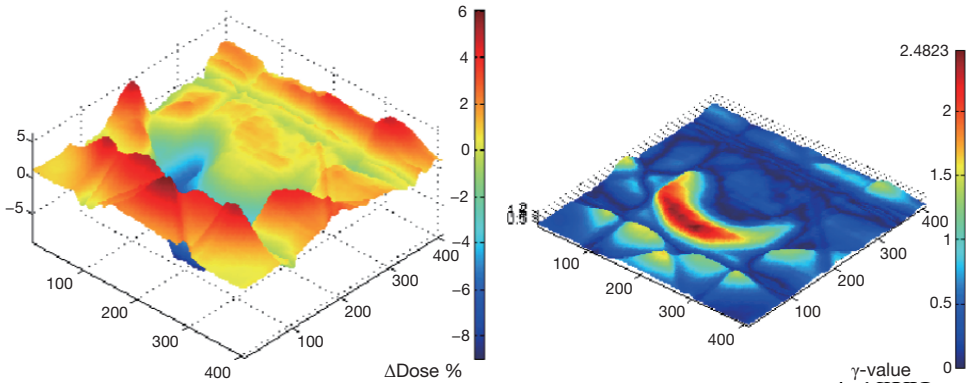

Figure 4 2D-γ maps plotted on the axial views for comparing plan 1 with plan 2. The red and blue coloring indicate that γ>1 (right panel) and are identifying as over/under estimated dose for pixels (left panel).

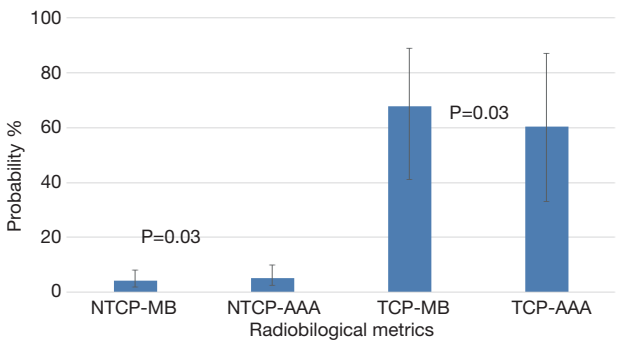

Figure 5 Results of TCP and NTCP radiobiological metrics from MB-PBC and AAA with 95% CI using bootstrap simulation with 1,000 replications. TCP, tumor control probability; NTCP, normal tissue complication probability; MB-PBC, Modified Batho method integrated with pencil beam convolution; AAA, anisotropic analytical algorithm.

consideration to meet the dose constraints when using plan 2 to treat the patient. However, the limit of this study is that we used the physical dose, DVH, to estimate the TCP/NTCP. In addition, uncertainty to estimate the radiological outcomes can occur due to the limit of model or radiobiological parameters (n, m and TD50). In this study, we used the more relevant parameters published for each algorithm, PBC or AAA, to minimize the over/underestimated values and to obtain the more accurate TCP/NTCP.

Conclusions

In this study, the plans recalculated with AAA yielded lower TCP with more NTCP than the plans calculated by MB-PBC. The radiobiological results were predicted using 2D gamma maps indicating a significate fraction of normal tissue or target would be respectively over/under dosed. However, a weak correlation was observed between the ΔTCP/ΔNTCP and the gamma passing rates with 2%/2 or 3%/3 mm criteria.

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Footnotes

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

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