Should the dose prescription be readjusted when using tissues density corrections algorithms for radiation oncology?

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Received October 20, 2014; Revised December 01, 2014; Accepted December 03, 2014; Published Online December 04, 2014

Editorial
Readjustment of prescription dose

Novel treatment planning systems (TPS), including new dose calculation algorithm, are continuously implemented in radiotherapy. The objective of this editorial is to alert the oncologists and physicists about the potential impact resulting from the use of any novel generation of dose calculation algorithms on the treatment dose representation. Along the same line, we provide arguments for discussion between oncologists and physicists about the need to readjust the prescribed dose related to tissues inhomogeneity correction, notably in case of significant difference of dose display.

Dose calculation algorithms for tissues inhomogeneity correction

Currently, numerous different algorithms are available to calculate the dose with tissues inhomogeneity correction. These algorithms can be categorized into two groups according to the electron transport calculation:\footnote{Chaikh A, Balosso J. Should the dose prescription be readjusted when using tissues density corrections algorithms for radiation oncology? \textit{J Case Rep Onc Ther} \textbf{2015}; \textit{1}(1):118.}

- **Type (a):** change in lateral transport of electrons is not modelled. In this case the primary dose contribution modelled using the equivalent path length correction and one dimensional convolution, along fan lines, with an exponential for scattered radiation. Example of this type is the method for density correction integrated with the Pencil Beam Convolution algorithm in Eclipse\textsuperscript{®} TPS, such as Batho’s density correction method (PBC-MB).
- **Type (b):** consider, with approximation, the transport of electrons such as the Anisotropic Analytical Algorithm, "AAA", implemented in Eclipse\textsuperscript{®} TPS and Collapsed Cone Convolution, "CCC", implemented with Pinnacle\textsuperscript{®} TPS.

Arguments and criteria to readjust the prescribed dose

The validation of the treatment plan in radiation oncology is based on the assessment of the dose calculation. Therefore, the expected, and even more the obtained, clinical results are related to the calculated dose. This relation is however relatively complex and is presently represented at best by the tumor control probability (TCP)/normal tissues complication probability (NTCP) sigmoid curve. The changes of the dose calculation algorithm raise the question of the discontinuity of the dosimetric representation provided to oncologists. When a new algorithm is implemented, the calculated and then the distributed doses can differ from those computed by a previous algorithm. Consequently the integration of a new dose calculation algorithm produces a risk to under/overestimates the dose in comparison to the previous one. The clinical consequences of such dosimetric alterations are further modulated by the position of the dose level in the TCP/NTCP curves as shown in Figure 1. At present, no standard recommendation exists about the modification of prescribed dose when moving from a current reference algorithm to new algorithms which turn on the inhomogeneity correction.

In this report we introduce three criteria to readjust the prescribed dose including dosimetric analysis, statistical analysis and global analysis. Hopefully, the right medical decision concerning the change or not of the prescribed dose, could be based on these three criteria. Figure 2 shows the structured decision process involving the three steps. Each step provides specific information about the difference between the former and new algorithm.
**Dosimetric analysis:**
The impact of the change of dose calculation algorithms on the monitor units and dose distribution was largely discussed and reviewed, i.e., the change from PBC, without heterogeneity correction, to heterogeneity correction using Type (a) dose calculation algorithm. In this case the treatment planning requires less monitor units (MU) (typically about 5% less) to deliver the prescribed dose to target volumes. The comparison of dose volume histograms showed, conversely, a greater dose for organ at risks. According to the specific TCP/NTCP balance of each case, this may result in an overall either better, or equal, or worse outcome. We suggest, with the *normalized method* using as input the MU calculated with the former algorithm, to recalculate the prescribed dose with the new algorithm most probably of the Type (b). To our opinion, this is a robust and reasonable method to obtain the reasonable clinical results that are based on Type (a) algorithms. In fact, the prescribed dose is the result of decades of cumulated clinical experience mostly based on Type (a) algorithms. Recently, the need to readjust the prescribed dose was confirmed in several publications especially when moving from Type (a) to Type (b) algorithms such as AAA. The calculated NTCP is also very sensitive to the choice of dose calculation algorithms. Bufacchi et al. showed that the NTCP associated with AAA was lower than NTCP associated with PBC when using the *normalized method* to recalculate with AAA.

**FIG. 1:** Plot of NTCP curve showing that 4% of dose differences result in 30% changes in normal tissue complication probability.

**FIG. 2:** Structured medical decision process involving dosimetric, global and statistic steps.
Global analysis:
The comparison of the spatial dose distribution using $\gamma$ or $\chi$-indexes requires two DICOM-RT files: one should be produced by the former algorithm and the other by the new algorithm. The global analysis displays the differences between dose calculation algorithms by $\gamma$ or $\chi$ maps showing a visualization of dose differences, and gamma voxel histograms showing the fractions of voxels having a specific $\gamma$ or $\chi$ value. In the case of the comparison of PBC algorithms when the inhomogeneity correction is turned off/on confirmed the results observed by dosimetric data. Figure 3 shows a comparison between isodose distributions calculated by PBC and PBC-MB with the global analysis based on gamma index for (3%, 3mm).

Statistical analysis:
In the case of the inhomogeneity correction using algorithm Type (a), significant dose differences were observed suggesting a dosimetric and clinical impact. However, to conclude as a significant difference, a certain number of patient’s cases and the use of the right statistical test are critical needs. As usual, the first step to carry out a statistical analysis is to know a priori the number of patient needed for the proper sample size ($n$) to achieve a $p$-value < 0.05. The $p$-value < 0.05 implies a significant, in other words "a real", difference between dose calculation algorithms. There are several methods to estimate the number of patients. More recently, Chaikh et al., presented two methods to estimate the number of patient based on bootstrap method and statistical power method. In this study, authors used the power method to determine the sample size. It is interesting to know that before estimating the sample size, a significance level ($\alpha$) and the statistical power should be required. The $\alpha$ is typically set to 0.05 showing the probability of "erroneously" to conclude a real difference between the dosimetric data. In the case of radiation oncology, the statistical power shows the probability of "correctly" conclude to a real difference between dosimetric data. A conventional choice of power is either 80% or 90%. We evaluate the sample size needed to assess a mean dose difference ($d$) of 1%, 2% or 3% with a standard deviation of 3SD. Assuming that the data had a normal distribution, the 3SD cover 99% of the data and the probability $\alpha$ is 0.05. Figure 4 shows a plot of statistical power according to the sample size using PS software for paired test with SD=3 and mean dose difference ($d$) equal to 1, 2 and 3%. It can be seen, in Figure 4 with $d$ =1%, that it requires about 75 patients to achieve 80% power, i.e., to be able to reject the null hypothesis with a power equal to 0.8.

FIG. 3: Comparison between isodose distributions calculated by PBC and Batho’s density correction method (PBC-MB) with the global analysis based on gamma index for (3%, 3mm), from Chaikh et al.
In conclusion, the dosimetric effect of heterogeneity depends on tissues densities, trajectory lengths of the beam, energy, field size, dose calculation algorithm including Type (a), Type (b) or more recently Type (c) such as Acuros XB algorithm \(^5\), and finally the clinical effect depends of the alteration of the TCP/NTCP balance induced by those dosimetric effect in each case. Therefore, the heterogeneity correction is able to introduce significant differences for dose calculation in low density tissues, as in chest. The comparison of dose calculation algorithms for inhomogeneity correction using the three criteria, dosimetric, global and statistic is able to show the likelihood of the need of dose prescription adjustment, as well as, the dose constraints to validate the treatment planning for inhomogeneity correction and to improve the expected clinical results.\(^5\)

**References**


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