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# What should we know about photon dose calculation algorithms used for radiotherapy? Their impact on dose distribution and medical decisions based on TCP/NTCP

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*Review Article*

## Abstract

The dose calculation algorithms, integrated in a radiotherapy treatment planning system, use different approximations to swiftly compute the dose distributions. Any biological effect is somehow related to the dose delivered to the tissues. Thus, the optimization of treatment planning in radiation oncology requires, as a basis, the most accurate dose calculation to carry out the best possible prediction of the Normal Tissue Complication Probability (NTCP), as well as Tumor Control Probability (TCP). Presently, a number of bio-mathematical models exist to estimate TCP and NTCP from a physical calculated dose using the differential dose volume histogram (dDVH). The purpose of this review is to highlight the link between any change of algorithms and possible significant changes of DVH metrics, TCP, NTCP and even more of estimated Quality-adjusted life years (QALY) based on predicted NTCP. The former algorithms, such as pencil beam convolution (PBC) algorithm with 1D or 3D density correction methods, overestimated the TCP while underestimating NTCP for lung cancer. The magnitude of error depends on the algorithms, the radiobiological models and their assumed radiobiological parameters setting. The over/under estimation of radiotherapy outcomes can reach up to 50% relatively. Presently, the anisotropic analytical algorithm (AAA), collapsed cone convolution algorithm (CCC), Acuros-XB or Monte Carlo are the most recommended algorithms to consistently estimate the TCP/ NTCP outcomes and QALY score, to rank and compare radiotherapy plans, to make a useful medical decision regarding the best plan. This paper points out also that the values of the NTCP radiobiological parameters should be adjusted to each dose calculation algorithm to provide the most accurate estimates.

**Keywords**: Dose calculation algorithm, Radiobiological models, Medical decision.

## 1. Introduction

The advance and development in radiation therapy offers substantial improvement in clinical accuracy in term of delivered dose compared with former calculation methods. The delivered dose should be calculated with a dose calculation algorithm integrated into a treatment planning system (TPS) connected to the irradiation machines, mostly linacs. This advance allows to deliver more exactly the desired prescription dose to maximize the Tumor Control Probability (TCP) for targets while minimizing the dose to normal tissues, thus minimizing the Normal Tissue Complication Probability (NTCP) for organs at risk (OARs). The International Commission on Radiation Units and Measurements (ICRU) has recommended an overall dose accuracy within ± 5%.[1] Considering the other uncertainties resulting from patient setup, delineation,

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machine calibration, it is necessary to have a dose calculation algorithm that can predict dose distribution within less than 3% accuracy. In this case, considering 3% uncertainty from dose calculation, is resulting in an overall uncertainty of 5.1% for the present state of the art and 3.8 % for future development.[2] However, for a decade, the dose was calculated using Clarkson or pencil beam convolution (PBC) methods without heterogeneity correction. The more accurate algorithms account for the heterogeneity correction of tissues.[3-8] Nowadays, a clinically relevant quantification of radiotherapy plans can be obtained with radiobiological models as those computing TCP and NTCP.[9] However, there is a considerable risk that the TCP/NTCP prediction calculated with recent algorithm are computed applying former radiobiological parameters established for older algorithms. In this paper, we raise the questions about the validity of clinical/radiobiological parameters; which algorithm can be used to rank radiotherapy plans using TCP/NTCP scores; and what is the correct way of estimating TCP/NTCP values if the medical decision is based on radiobiological outcomes?

There are two folds for answering these questions. Firstly, the most important one is the dose calculation algorithm. Nevertheless, the problem is that an improved accuracy in the dose calculation does not necessarily yield an improved accuracy of the predicted NTCP. Thus, the second fold is radiobiological models. These models are based on the previous and less precise algorithms combined with old clinical outcomes. In this paper, we address the methods to manage this issue and take with confidence the right medical decision to compare and rank radiotherapy plans to select the best treatment for patients.

## 2. Dose calculation models

A radiotherapy X-Ray beam contains a spectrum of primary photons originating directly from the target hit by the primary accelerated electrons, extra-focal head-scattered photons produced by the primary photons interacting in the accelerator head and the contaminating charged particles, secondary electrons, produced in these interactions. The dose deposited into the patients can be divided into primary dose and secondary dose. The dose deposited by the charged particles (electrons) launched by the direct photons first interactions, in the tissues, is referred to as the primary dose. The dose deposited as a consequence of scattered photons interactions is called the secondary dose or scattered dose. The dose deposition is influenced by the density of the tissues and its variations according to the anatomic properties of the body. These heterogeneities are therefore an important concern for dose calculation. However, there are various methods to take account for the heterogeneities correction of tissues.[2,10] We will categorize these methods into two categories: methods based on empirical inhomogeneity correction factor (CF) and methods based on superposition convolution (SC).

### 2.1. Methods based on empirical inhomogeneity correction factor

These methods take into account tissues density information either in one-dimensional (1D) or the full three-dimensions (3D) of along a ray path from the source to the point interest. The inhomogeneity's correction are handled by an equivalent path length (EPL) scaling, Batho Power law (BPL), Modified Batho's (MB) density correction or equivalent tissue-air ratio (EqTAR). Basic tissues density information are drawn from CT-scan (tomodensitometry) Hounsfield-units.

#### 2.1.1. EPL method

Tthe EPL algorithm uses a 1D convolution method which takes into account the heterogeneities along the fan lines of the beam. It does not account for inhomogeneity that is present across or lateral to the beam direction. It rescales the depth of the inhomogeneity by accounting for the density of the medium involved. The correction factor is applied on the primary photon beam kernel and not on the scattered photon kernel. This model calculates the change in the primary energy fluency at the depth of dose calculation due to the presence of heterogeneity.[2] The density averaged depth at the point of calculation at a physical depth z is given by :

$$z' = \frac{1}{\rho_w}\int_0^z \rho(z'')dz'' \qquad (1)$$

where $\rho_w$ is the density of water and $\rho(z'')$ is the density at local depth (z") which is calculated from CT-scan images. Thus, the dose is corrected by replacing the calculated EPL (z').

#### 2.1.2. BPL and MB methods

The correction factor suggested by Batho as an empirical correction to account for both primary beam attenuation and scatter changes within water and below a single slab of lung material with density relative to water of 0.35.[11] Sontag and Cunningham generalized the method to handle arbitrary densities and non-water like materials[12]. Later, Webb, Fox and Cassell *et al.,* went further to allow for multiple regions of slab-like materials.[13,14] Finally, El-Khatib and Thomas showed that the correction factor should be based on build-up depth-shifted Tissue Maximum Ratio **(**TMR) instead of the initially proposal using Tissue Air Ratio **(**TAR) [15,16]:

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$$CF = (\mu_{en}/\rho)_N / (\mu_{en}/\rho)_W \prod_{m=1}^{N} (TMR(z-z_m+z_{bu}))^{(\mu_m-\mu_{m-1})/\mu_w} \quad (2)$$

where, $\mu_m$ and $\mu_w$ are the linear attenuation coefficients of the material in layer m and water respectively; $Z_{bu}$ is the build-up depth and $Z_m$ is the distance along the beam from the surface to the layer m in the phantom.

### 2.1.3. EqTAR

The correction factor proposed by Sontag *et al*, allows to correct the inhomogeneities in the patient anatomy in 3D density data.[17,18] This method applies a ray trace to determine the change in the primary dose and calculate the scatter dose. EqTAR method is based on the density-scaling theorem. For heterogeneity correction, this method use TAR dependent on the effective beam radius (ρr) to take account of scattered radiation and effective depth (ρd) for primary beam correction. This means the depth and the radius are scaled according to the relative electron density of the heterogeneous medium. The correction factor is given by:

$$CF = \frac{TAR(\rho d, \rho r)}{TAR(d, r)} \quad (3)$$

## 2.2. Methods based on superposition convolution

Photons can travel large distances and the energy and direction of a primary photon is independent of where it interacts. The energy deposition by secondary particles around a primary photon interaction can be described by a "kernel". Energy deposition kernels are defined as the distribution of energy imparted to volume elements (per unit volume) in a medium, commonly water, due to an elemental photon beam interaction at the origin of the coordinates of the kernel. Energy deposition kernels are categorized according to the geometry of the elemental beam that delivers the incident energy: Point kernel describing the pattern of energy deposited in an infinite medium around a primary photon interaction; or pencil kernel describes the energy deposition in a semi-infinite medium from a point mono-directional beam and a planar kernel describes the forward and backward energy spread from primary interactions located in a plane, laterally oriented in an infinite broad beam.[2] Figure 1 shows the irradiation geometries for point kernels, pencil kernels and planar kernels. The isodose curves are shown as full curves.

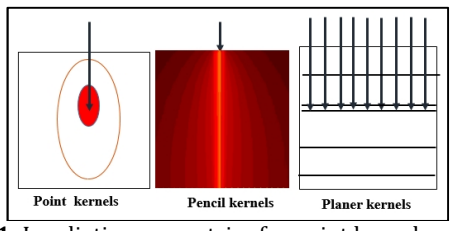


**Figure 1:** Irradiation geometries for point kernels, pencil kernels and planar kernels. The isodose curves are shown as full curves (from Anders *et al.* [2]).

### 2.2.1. Point kernels models

The calculation of dose from point kernels can be described as a two-steps procedure. In the first step, the energy released in the patient through attenuation of the primary photons is calculated by ray-tracing primary photon trajectories, including beam modulators, etc. The ray-trace is normally performed with interaction data mapped from CT scans to represent the patient. In the second step, dose is calculated by superposition of appropriately weighted kernels. To take account of the heterogeneity the common approach is the scaling of all dose fractions of a point kernel $h\rho_0$, calculated for a homogeneous medium of mass density $\rho_0$, by the mean electron density between the point (s) of energy release and the point (r) of energy deposition, i.e, as:

$$h_{het}(s,r) = \frac{\rho(r)}{\rho_0} c^2 h\rho_0[c(r-s)] \quad (4)$$

$$c = c(s,r) = \int_0^1 \rho_{rel}[s - l(s-r)]dl \quad (5)$$

$\rho_{rel}$ is the relative number of electrons per volume as compared with the reference medium.
Then the dose can be calculated as:

$$D(r) = \iiint_v T(s) \frac{\rho(s)}{\rho_0} c^2 h\rho_0[c(r-s)]d^3s \quad (6)$$

One of the disadvantages in using a point kernel is that it is quite time consuming. Several methods can be used for direct summation of density scaled kernels in dose calculations. These methods include the use of Fourier transforms, correction factor and Collapsed Cone Convolution (CCC). For CCC, Ahnesjo *et al.* 1989, applies an angular discretization of the kernel which enables an efficient approach for energy transport and deposition.[19,20] Angular discretization of a parameterized point kernel yields, for each discrete angular sector (cone) i, the energy deposition per radial distance as:

$$h(r,\Omega) = (A_\Omega e^{-a_\Omega r} + B_\Omega e^{-b_\Omega r}) / r^2 \quad (7)$$

where, $A_\Omega$, $a_\Omega$, $B_\Omega$ and $b_\Omega$ are fitting parameters depending on the scattering angle Ω. The first term describes the primary dose and the second term describes scatter dose.

### 2.2.2. Pencil beam kernel models

The pencil kernel describes the energy deposited in a semi-infinite medium from a point mono-directional beam. For the purpose of treatment optimization, Gustafsson *et al* [21] used a formulation for radiotherapy dose calculation:

$$D(r) = \iint_{s} \int_{E} \iint_{\Omega} \sum_{m} \Psi^{m}_{E,\Omega}(s) \frac{p^{m}}{\rho}(E, \Omega, s, r) d^{2}\Omega \, dE \, d^{2}s \quad (8)$$

Where $\Psi^{m}_{E,\Omega}(s)$ is the energy fluency differential in energy E and direction Ω for beam modality m and $\frac{p^{m}}{\rho}(E, \Omega, s, r)$ is the corresponding pencil kernel for energy deposition per unit mass at *r* due to primary particles entering the patient at *s*.

Ahnesjo *et al.*[22] expressed that pencil kernels in cylindrical coordinates (r,z) can be accurately calculated as:

$$\frac{p}{\rho}(r, z) = \frac{A_{z} e^{-a_{z} r} + B_{z} e^{-b_{z} r}}{r} \quad (9)$$

where, $A_z$, $a_z$, $B_z$ and $b_z$ are functions of depth.

Pencil kernel models are effectively hybrid algorithms that fully account for beam modulations and field shapes but rely on broad beam scaling/correction methods to handle heterogeneities and patient characteristics. Provided fluencies and kernels are properly normalized, the dose is calculated in absolute units that can be used to derive output factors. The two main accuracy limitations of pencil kernel models are for heterogeneities and for scatter dose calculations in patient sizes.[23, 24]

### 2.3. Monte Carlo dose calculation method

The Monte Carlo (MC) dose calculation method is the most accurate algorithm and has always been used to compare the dose distributions with dose calculation algorithms. The MC method uses photon and electron transport compounds to consider the trajectories of individual particles and thus the pattern of dose deposition. Each particle history is determined by the random number generator and millions of particles histories are traced. Thus, MC calculations are very much time consuming. The dose distribution is built by summing the energy deposition in each particles history. This method models each photon interaction in the patient. MC method uses the photon interaction probabilities and has the potential to model the electron transport taking explicitly account for density correction. This method was used as an R&D tool and it will be used in future for clinical use. The use of MC-based methods is effective in some radiation oncology departments for the verification of TPS dose calculations.[25]

In this context, Acuros XB (AXB) uses a sophisticated technique to solve the linear Boltzmann transport (LBT) equation and accounts the effects of heterogeneities in patient dose calculations. AXB provides comparable accuracy to MC with improved calculation speed.

## 3. Dose calculation algorithms integrated in TPS

Numerous studies in the literature have categorized the dose calculation methods according to various criteria.[26-28] They classified the algorithms into three types according to whether they take into account, or not, the tissue density correction and include, or not, electron transport. In this review, we also chose to categorize the available methods into three types according to the concept used to take account of the tissues density correction. The Table 1 shows the available models and algorithms for radiotherapy. The Table 2 shows the methods for dose calculation algorithms and its ability to take into account the dose compositions for 1D or 3D heterogeneity correction tissues. The (+) shows that the algorithm take into account the corresponding dose component, but (−) shows that the algorithm does not take into account the corresponding dose component.

**Table 1:** The available models and algorithms for radiotherapy.

| Types | Models | Description | Algorithms in TPS |
|---|---|---|---|
| A | Inhomogeneity correction factor | -models do not account for changes in lateral electron transport.<br>-reconstructs measured dose by interpolating profiles and depth doses. | EPL<br>BPL, MB, EqTAR |
| | Pencil kernel | -methods superpose predetermined dose distributions from narrow pencils of radiation in water. | PBC |
| B | Point kernel | -calculates primary photons transfer energy to secondary particles.<br>-dose deposition from all secondary's handled by means of (pre-calculated, heterogeneity scaled) point kernels. | AAA<br>CS<br>CC |
| C | Grid based Boltzmann solvers | -calculates primary photons transfer energy to secondary particles. | AXB |
| | Monte Carlo | -simulates the fate of individual particles by using random numbers.<br>-calculation of primary photons transfer energy to secondary particles for variance reduction. | MC |

**Table 2:** Methods for dose calculation algorithms and their ability to take into account the dose component for 1D or 3D tissues heterogeneity correction. The (+) and (–) shows the level of performance of the different algorithms regarding the items listed in the table.

| Calculation methods | Algorithms | Dose compositions | | | Heterogeneity correction | Accuracy | Speed |
|---|---|---|---|---|---|---|---|
| | | Primary photons | Scattered photons | Contaminating electrons | | | |
| Primary with Scattered | Clarkson | + | + | - | none | + | ++ |
| Superposition Convolution | PBC alone | + | + | - | none | + | ++ |
| PBC with correction factor | PBC-EPL<br>PBC-MB<br>PBC-BPL | + | + | - | 1D | ++ | ++ |
| | EqTAR | + | + | - | 3D | ++ | ++ |
| Superposition Convolution | Pencil beam kernel (AAA) | + | + | + | 3D | +++ | ++ |
| | Point kernels CCC | + | + | ++ | 3D | ++++ | ++ |
| LBT | AXB | + | + | +++ | 3D | ++++ | + |
| MC | MC | + | + | +++ | 3D | +++++ | - |

## 4. Modernization of radiotherapy outcomes from the calculated dose

The Figure 2 shows the multiple outcomes to which the dose calculation algorithms are contributing in radiotherapy.

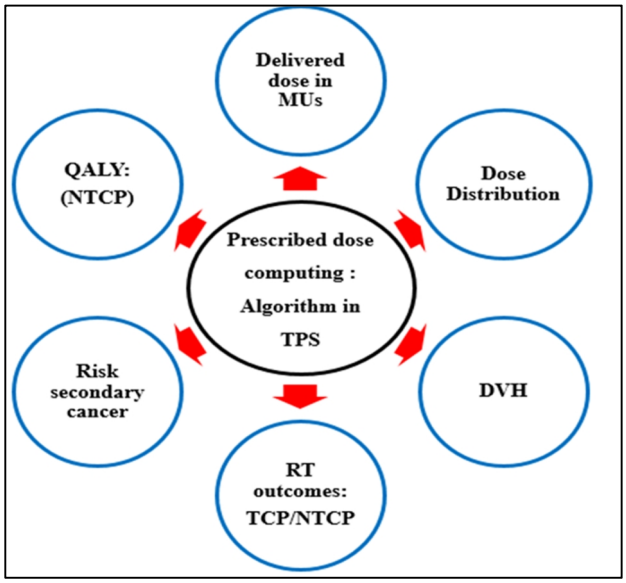


**Figure 2:** The main outcomes the dose calculation algorithms make possible to compute in radiotherapy.

### 4.1. Radiobiological evaluation

Both TCP and NTCP can be calculated using the differential dose volume histograms (dDVH). The main objective is to use the biological models to predict the RT outcomes, from the dose distribution, and to make these biological estimates as accurate as possible. For this purpose, biological models are now integrated in some TPS to compare RT plans, and thus to be able to rank them. Therefore, the DVH metrics can be used to evaluate the biological response and to predict the outcome of different plans. However, there are several biological models to predict TCP and NTCP.[29-44] The most common TCP model is the Poisson model with the Linear-Quadratic (LQ) equation. The most common NTCP models are the Lyman-Kutcher-Burman one (LKB), the relative seriality model (s) and the Equivalent Uniform Dose (EUD). These models are included in some TPS.[45] The Table 3 shows the most common TCP and NTCP radiobiological models integrated in TPS. One of the limit is that there is a variability of radiobiological parameters setting in the literature. The LKB model describes complication probabilities for uniformly irradiated whole or partial organ volumes. The cumulative distribution function of the normal distribution is chosen to represent an empirical sigmoid dependence of NTCP on dose. The shape of the NTCP relation is determined by three parameters: $TD_{50}$, m and n. $TD_{50}$ and m, describe the position of the sigmoid curve along the dose axis and curve steepness, respectively and n describes the magnitude of the volume effect using a power-law relationship between the tolerance dose and irradiated volume. The s-model describes response of an organ with a mixture of serial and parallel arranged Functional Sub-Units (FSUs). The relative contribution of each type of architecture is described by the parameter "s", which is equal to unity for a fully serial organ and zero for a fully parallel organ. Generalized gEUD can also be used to predict TCP/NTCP

from the physical dose, DVH, for treatment plan optimization and to rank treatment plans. Thus, the Uncomplicated Tumor Control Probability (UTCP) can be calculated as [46]:

$$UTCP = TCP.\ \Pi i\ (1\text{-}NTCPi) \qquad (10)$$

where, "i" includes the organs at risks that should be considered for each cancer site.
To rank a treatment plan, Langer *et al,* proposed the S-score [47,48]:

$$S\text{-}score = TCP.\ (1\text{-}NTCP) \qquad (11)$$

When the absolute value of NTCP is large, the score will be very sensitive to the changes in NTCP, but when the absolute value of NTCP is small, the score will be relatively insensitive to changes in NTCP. To avoid this problem, Brenner et al proposed a R-score, defined as:

$$R\text{-}score = TCP / NTCP \qquad (12)$$

### 4.2. Quality adjusted life years (QALY) score

In order to quantify the real benefit of the treatment for the patient a combination of survival and quality of life (QoL) is provided by the QALY, the physical NTCP predicted from dDVH should be calibrated and multiplied with the "Utility value", calculated as[49]:

$$NTCP_{(QALY)} = NTCP * U\{I = 1 \text{ to } m\} \qquad (13)$$

where, U varied from zero to 1, including age, the number of years of survival expected as a benefit of the radiotherapy cure, grade, etc.

### 4.3. Secondary cancer risk estimation

The risk of secondary cancer is a rising concern among the growing population of patients having been cured of a first cancer. In the recent years, models of the risk of secondary cancer have been proposed and integrated in TPS.[74] As for other radiobiological estimates, the estimation of the 2nd cancer risk for a specific organ could be derived from DVH metrics using the organ equivalent dose (OED) model. The OED for a bell shaped risk relationship can be calculated as[75-77]:

$$OED_{org} = \frac{1}{N}\sum_{i=1}^{N} D_i e^{-\alpha_{org} D_i} \qquad (14)$$

where, N is dose calculation points, $D_i$ is the corresponding absorbed dose and $\alpha_{org}$ is an organ-specific parameter related to the dose-response derived from the fitting of the model to the Hodgkin's cohort data.

**Table 3:** The most common TCP and NTCP radio biological models integrated in TPS.

| Models | Structure type | Parameters | Equations |
|---|---|---|---|
| TCP<br>Poisson –LQ | Target | $TD_{50}$, γ, α/β, seriality(s), T1/2 for short vs. long repair time, parameters of tumor repopulation: Tpot and Tstart | $TCP = \prod_{i=1}^{M} P(D_i)^{v_i}$<br>$P(D_i) = \exp\left(-\exp\left(e\gamma - \alpha D_i - \beta \frac{D_i^2}{n}\right)\right)$ |
| NTCP<br>S-model with<br>Poisson –LQ | OAR | s = 1 serial organ<br>s = 0 parallel organ | $NTCP = \left[1 - \prod_{i=1}^{n}\left[1 - P(D_i)^s\right]^{v_i}\right]^{1/s}$ |
| NTCP<br>Lyman | OAR | $TD_{50}$, m, n, α/β | $NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e\frac{x^2}{2}dx$<br>$t = (Deff - TD_{50})/(mTD_{50})$<br>$Deff = \left(\sum_i v_i D_i^{1/n}\right)^n$ |
| EUD | Target<br>OAR | $TCD_{50}$, a ,γ50, α/β<br>$TD_{50}$, a ,γ50, α/β | $TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma 50}}$<br>$NTCP = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{4\gamma 50}}$<br>$EUD = \left(\sum_i v_i D_i^a\right)^{1/a}$ |

The OED is defined as the uniform irradiation dose of an organ that will yield the same secondary cancer risk as the inhomogeneous dose-distribution on which the OED-calculation is based. The secondary cancer risk is

by definition dependent on the OED and can be calculated as:

$$I^{org} = I_0^{org} \cdot OED_{org} \quad (15)$$

where, $I_0^{org}$ is the organ-specific secondary cancer incidence related to low-dose exposure e.g. as provided by the Life Span Study (LSS).[78]

## 5. Impacts of the changes of dose calculation algorithms on the delivered dose and radiotherapy outcomes

### 5.1. Influence of dose calculation algorithms on the delivered dose and monitor unites

The change of TPS algorithm, still prescribing the same dose, leads to two dose related effects. Firstly, the delivered dose at the isocentre will change due to the fact that a different number of monitor units (MUs) will be calculated. Secondly, the relative dose distribution will change showing a spatial variation in dose distribution. Chaikh *et al*, proposed a normalized MUs method to compare different dose calculation algorithms.[50,51]

The Figure 3 shows a method to compare the dose calculation algorithms and readjust the prescription dose using "fixed monitor units normalization" method. This method is based on the use of MUs from former algorithm, as input, and keeping the same field geometry and beam arrangement to re-calculate the dose with the newer one. To measure the magnitude of dose difference a 2D gamma maps was also proposed.[52] The Figure 4 shows the MUs calculated from PBC, PBC-MB and AAA normalized to 100%. The MUs were calculated for the same patients using the same prescribed dose and beam arrangement. The calculated dose to 95% of the target volume (D95%) in Figure 4 was firstly calculated with PBC and re-calculated with AAA, CCC and MC, using MUs from PBC, as input. The PBC was taken as the reference one, to show the impact on prescribed dose when moving to new generations of TPS.[53,54] The results from Figure 4 confirm that the PD should theoretically be readjusted by the radiation oncologist using the new algorithm. When the fixed MUs normalization is used to recalculate the PD at the isocentre inside the PTV or D95% from dose volume histograms, both PD and D95% were significantly different, especially for thorax irradiation, due to the most important heterogeneities of tissues' density in the thorax. In this context, a readjustment should be considered for thorax irradiations when moving from PBC to 1D or 3D density correction methods, such as PBC-MB, PBC-BPL or PBC-EqTAR. Then another re-adjustment of -5% should be done when moving from PBC with 1D/3D density correction methods to AAA.[55] It worths to be mentioned that the modification of PD varies in opposite senses in these two former situations, which can confuse the user! We recommend a local comparison of the algorithms since the differences depend also on the habits of use, of beam arrangements, energy and normalization of PD.

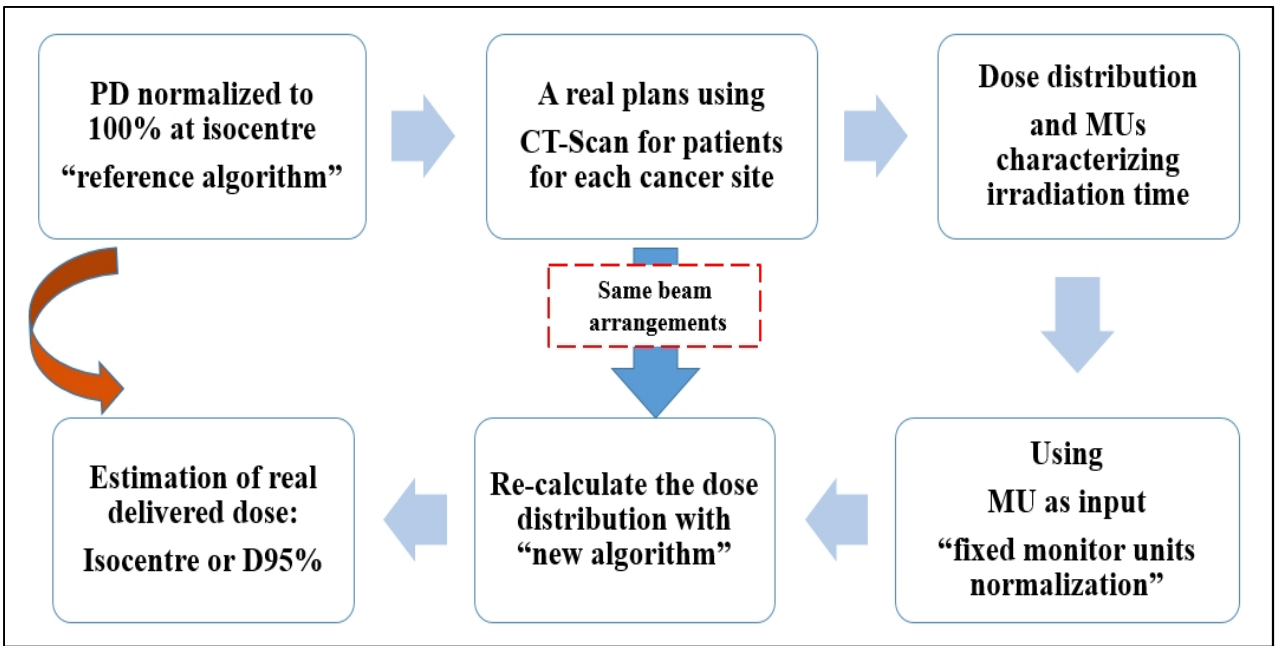


**Figure 3:** A method to compare the dose calculation algorithms and readjust the prescription dose (from Chaikh *et al.* [26]).

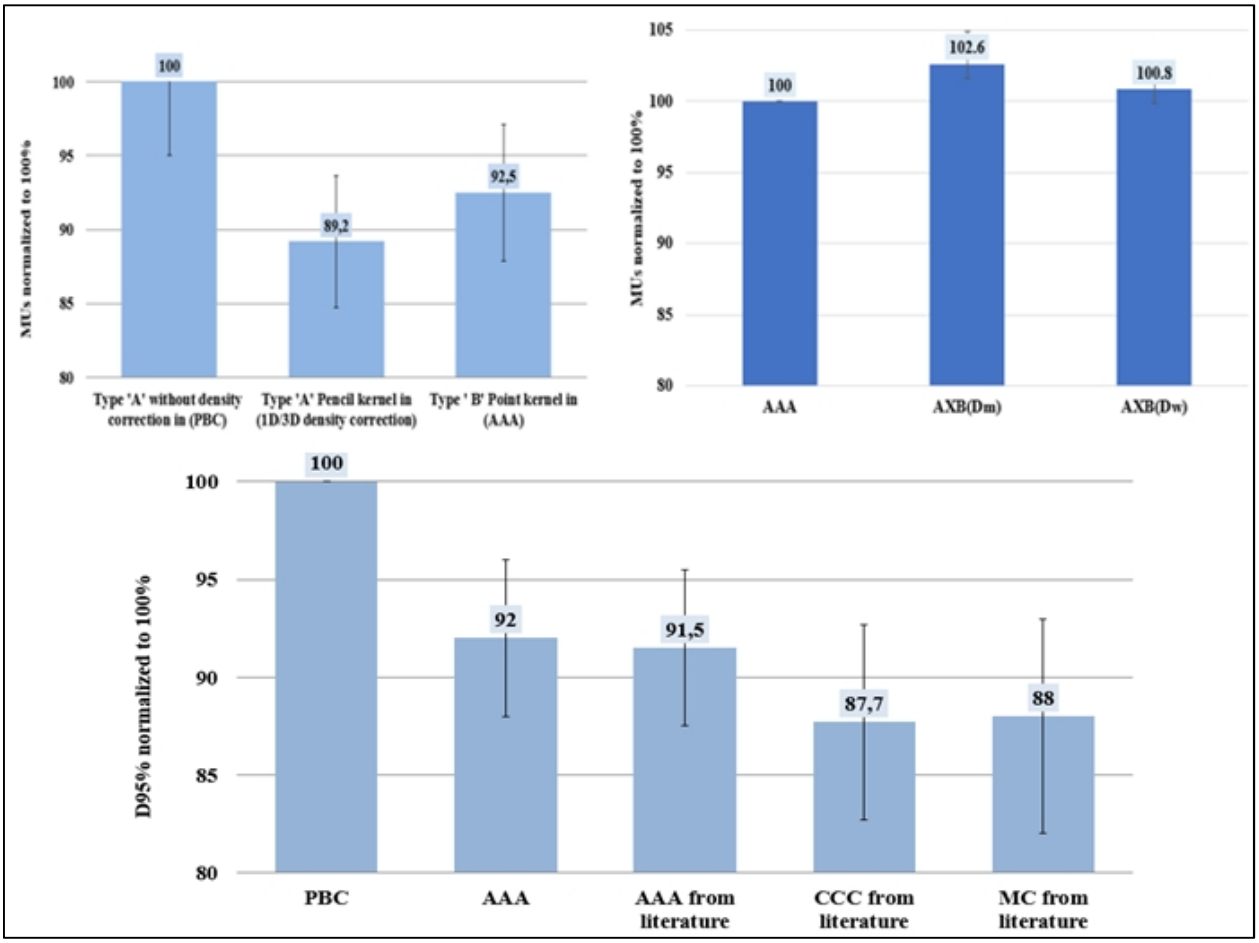


**Figure 4:** Normalized MUs and calculated dose to 95% of target (D95%) using types 'A', 'B' and 'C' algorithms for lung from RT-3D. The left upper panel shows the MUs normalized to 100% with PBC taken as the reference one vs types 'A' and 'B', respectively with MB and AAA. The right upper panel shows the MUs normalized to 100% with AAA taken as the reference one vs type 'C' as AXB(Dm) indicating dose to medium or AXB(Dw) indicating dose to water. The MUs were calculated for the same patients using the same prescribed dose and beam arrangements. The D95% were recalculated using MUs from PBC as input (from literature).

### 5.2. Influence of dose calculation algorithms on TCP/NTCP outcomes

The impact of the change of dose algorithms on tumor coverage, TCP or NTCP, has been investigated by several studies.[56-67] The American Association of Physicists in Medicine (AAPM) report number 85 on tissue inhomogeneity corrections mentioned that a 5% change in dose might result in a significant change in TCP and NTCP. The studies reported that the photon dose calculation algorithm has a significant impact on radiobiological metrics. They showed that the re-evaluation of NTCP model parameters is necessary when more accurate dose data are available to avoid over or underestimated NTCP. Chetty, *et al*, showed that an average TCP decrements up to 50%, can be observed with the EPL model. Liu, *et al*, also reported that EPL overestimates TCP by 20-50%. Chaikh, *et al.* 2016, reported that the TCP/NTCP is strongly affected by the wide-ranging values of radiobiological parameters and the differences between the dose distributions from various algorithms yield statistically differences in both TCP and NTCP values. For instance, they showed that NTCP values for pneumonitis are very sensitive to the choice of the algorithm, as they are to the dose constraints: V20 Gy, V30 Gy, and mean dose.

#### 5.2.1. Sensitivity of radiobiological parameters settings with the change of dose calculation algorithm

For both LKB and s-model, presented in this study, the need to readjust clinical parameters due to the change of dose calculation algorithm is reported by several studies, and the shifts of these parameters were also published. Lung pneumonitis as endpoint has been chosen as the focus of the present paper, because the differences of doses calculated by the algorithms, of types 'A' or 'B' and 'C', have a large impact on the dose distributions in the highly inhomogeneous thoracic region due to lower lung density. Nevertheless, the most important effect is when moving from type 'A' to type 'B'. This effect can be found in other anatomical regions;

however, the magnitude of changes is depending on target location. Therefore, should the user use the TCP/NTCP to rank treatment plans using published data, he/she will introduce extra uncertainties leading to over/under prediction of TCP/NTCP values. Thus, one should check that the parameters are well adapted to the used algorithm type. In this context, we advise the use of the recommended radiobiological setting for the adapted algorithm. The Table 4 shows the compilation of the radiobiological settings, for lung pneumonitis, for several dose calculation algorithms.

**Table 4:** The suggested radiobiological settings for lung pneumonitis for several dose calculation algorithms.

| Literature proposals | n | m | $TD_{50}$ (Gy) |
|---|---|---|---|
| Initial data[68,69] | 0.87 | 0.18 | 24.50 |
| Grade ≥ 2[70] | 0.99 | 0.37 | 30.8 |
| Grade ≥ 2 with NTD[71] | 1 | 0.3 | 30.5 |
| EPL[72] | 1.0 | 0.45 | 34.1 |
| CS[72] | 1.0 | 0.45 | 29.2 |
| PBC[73] | 0.99 | 0.37 | 30.78 |
| AAA[73] | 0.99 | 0.374 | 29.19 |

### 5.2.2. Clinical utility of TCP/NTCP to compare radiotherapy plans

The present review establishes one example of the general need to change the parameters values according to the algorithm types and to define a level of NTCP in absolute and relative values, to rank treatment plans to select the best one to treat a patient. The Figure 5 shows the NTCP values, as an example, from the treatment of a lung cancer with prescription doses varying from 50 to 66 Gy. The NTCP were estimated using LKB model and bootstrap simulation method based on 1000 replications for lung radiation pneumonitis. For all NTCP calculations the AAA-calculated DVH was used as input data. The NTCP values were obtained using the radiological parameter settings given in Table 4.

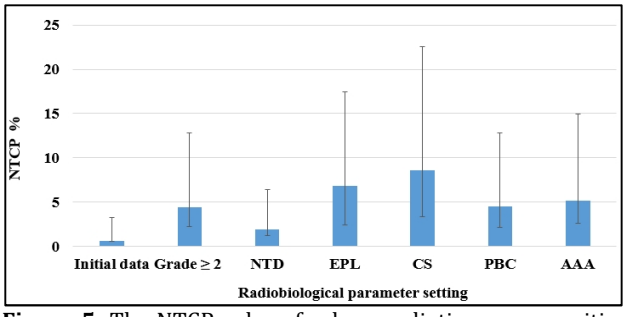


**Figure 5:** The NTCP values for lung radiation pneumonitis from treatment of lung cancer. The NTCP were estimated with LKB model using the various radiological parameters setting given in Table 4. The DVH in any case was calculated using AAA .

Assuming AAA is closer to the physical reality, the NTCP estimated with AAA adapted parameters yield about 5%, although NTCP calculated with CS parameters yields overestimated NTCP absolute values > 10% and NTCP calculated with the "initial data" are very low <5% and probably underestimated. Thus, in this case, the variation of absolute NTCP is clinically questioning.

It is, however, not the NTCP itself that is presently our main interest, but the critical need to adapt the NTCP parameters to the dose calculation algorithm used for the treatment planning. On the other hand, the ΔNTCP, as relative values, could reach 50%, depending on the model parameter values.

### 5.3. Influence of dose calculation algorithms on QALY score

Since, the predicted TCP/NTCP depends on the performance of dose calculation methods, as mentioned above, the comparison of DVH metrics should be carried out using the most accurate dose calculation algorithms, and after a major effort to optimize the plans. Then, for PTV and OARs, the DVH metrics can be used to select the better plans by comparing TCP/NTCP and UTCP. As an example, AAA shows a significant difference compared to pencil beam density correction methods (PB-MB or EPL). The relevant lung TCP/NTCP data show lower TCP and higher NTCP with AAA compared to MB. Using the data from MB will probably significantly overestimate the predictive QALY, justifying the use of more accurate algorithms.

### 5.4. Influence of dose calculation algorithms on second cancer risk estimation in radiotherapy

The dose calculation algorithms use different approximations to compute the dose distributions. The shift on DVH bins resulting from the change of algorithm can influence the OED values. Since the more advanced algorithms predicted a significant dose difference to OARs, the OED will be significantly over/under estimated predicting more/less risks compared to former algorithms. Thus, the use of dose calculation method that compute the dose using primary dose with scatter dose would yield wrong results for secondary cancer risk estimation, since the dose distribution from electrons transport is very important, especially in thorax region including breast, lungs and esophagus. The risk of secondary cancer for young patients is more important than for aged patients, this risk should be properly estimated in children by using more accurate algorithms showing the best, if not "real", DVH. For example, in paediatric medulloblastoma with RT-3D, the AAA yield more average dose for lung compared with PBC-MB. Thus, the OEDs for lung from a bell shaped risk relationship model, equation 14, with $\alpha_{lung}$ = 0.129 were 1.84 Gy and 1.72 Gy using respectively, AAA and PBC-MB. A significant difference for DVH for thorax organs could also be observed using 18 MV compared to 6 MV depending on the performance of algorithm.
In addition, for proton radiotherapy, the algorithms should also integrate the contribution of neutron contamination of proton beam. For example, when irradiating the brain with proton therapy the neutron

contamination could potentially increase the radiation-induced secondary tumors.

## 6. Discussion

The former radiobiological parameters such as γ, n, m, $TD_{50}$, etc. were validated using clinical data obtained with the less accurate type 'A' algorithm. Hence, using these former clinical data to recalculate the TCP/NTCP using, as input, DVH calculated with the latest algorithms will introduce errors for estimated TCP/NTCP. The application of readjusted parameters adapted to these updated algorithms, for each specific model, will result in more accurate TCP/NTCP. In this paper, we reviewed the commonly used dose calculation algorithms types. We showed that significant dose differences could be observed either for DVHs for target volumes or OARs introducing considerable over/under estimations of TCP/NTCP metrics. However, the comparison of treatment plans using the former clinical data might be useful to estimate the magnitude of uncertainties for the model parameters values. The uncertainties can be evaluated and presented as confidence interval using bootstrap simulation method. We advise that the change of dose calculation algorithms should be performed with a lot of care since the clinical knowledge's are based on the former algorithms and the new algorithm will need more accurate NTCP parameters.

We advise, if possible, to locally calibrate a radiobiological model to better predict the toxicity. One of the solution is to correlate a kind of integrated measure of the Qol with the calculated toxicity. In this context, we can consider two categories of toxicity:

- The first category includes a moderate toxicity, the "acceptable risk of radiations", which does not affect Qol of the patient. In this case, a local calibration of the parameter setting could be carried out, or a simple estimation of NTCP could be done using published data. In this case, the calibration should only include the toxicity related to irradiation, e.g. cataract or trouble of vision, but the Qol could be rather insensitive.

- The second category includes "unacceptable risk of radiations" which affect the Qol of the patient. In this case, the risk cannot occur without delivering a certain amount of radiations to OARs, and the Qol could be significantly altered leading to a considerable impact, like complete blindness, or even death by severe radiation pneumonitis. In these cases, one must limit the radiation dose to the OARs in order to avoid these effects. This could need to decrease the delivered dose to the tumor target and thus altering the TCP. In this case, a reliable balance between TCP and NTCP prediction should be available. For this, beyond the use of the most updated dose calculation algorithms and the most adapted radiobiological parameters, as mentioned before, weighting factors taking account of the age and the comorbidities of the patients should ideally be associated to this balanced prediction of outcome. This is presently mainly the radiation oncologist experience that allows this compromise.

**Table 5:** A list of TPS and algorithms for dose calculation tested by the IROC Houston through the irradiation of the lung phantom.

| TPS | Algorithm |
|---|---|
| Accuray Multiplan | MC |
| Accuray TomoTherapy | CS |
| Brain Lab IPlan | MC |
| Elekta Monaco | XVMC or CCC |
| Elekta XiO | Multi-grid Superposition or Fast Superposition |
| Phillips Pinnacle | CCC or Adaptive Convolve |
| Prowess Panther | CCC |
| RaySearch RayStation | CCC |
| Varian Eclipse | AAA or AXB |
| Helax | CC |
| Nomos Corvus | MC |

Abbreviations: MC: Monte Carlo; CS: Convolution Superposition; CCC: Collapsed Cone Convolution; CC: Collapsed Cone ;AAA: Anisotropic Analytical Algorithm; AXB: Acuros-XB

### 6.1. Dose uniformity for lung cancer with heterogeneity correction with types A and B algorithms

The DVH is the base to compute the TCP/NTCP metrics. In this section we will discuss about the alterations of DVH which could be observed when moving from PBC without heterogeneity correction to correction-based pencil beam type 'A' then type 'B' and type 'C' algorithms. Firstly, the shape of DVH is very sensible to dose calculation algorithms, photon energy and irradiation techniques. In this context, the former algorithms such as PBC, PBC-MB, PBC-EqTAR have more limited accuracy for modeling the dose in the target and OARs. They overestimated the dose distribution in the target and thus TCP/NTCP. The PBC predicted more homogeneous dose distribution compared with type 'B' and 'C' algorithms. Using the most accurate algorithms, such as AAA, AXB or MC, the dose distribution is more heterogeneous compared with type 'A' algorithms. The dose heterogeneity inside the PTV will introduce either "cold spots" or "hot spots". For example, AAA predicted more heterogeneous dose than MB, as mentioned above. Secondly, the dosimetric parameters, derived from DVH can be significantly changed. Consequently, this will lead to over/under estimating of EUD and TCP score as well

as NTCP. For example, PBC alone, or with density correction methods, erroneously predicts a higher dose in the beam entrance around the tumor located in the lung and overestimated the tumor coverage and TCP, compared with AAA.

### 6.2. Recommended algorithm for dose calculation in clinical use

The CCC and AXB are superior to the PBC and type 'A' in terms of accuracy of the calculated dose and these algorithms would be recommended to compare and rank radiotherapy plans. More recent studies showed that AAA overestimates the PTV dose and TCP compared to AXB. The difference can reach up to 5.8 % for TCP, while both algorithms yield very similar NTCP on lung pneumonitis based on the LKB model parameter.[79,80] Table 5 shows a list of TPS and algorithms for dose calculation, recommended by the IROC (M.D. Anderson, Houston) through the irradiation of a lung phantom.[81]

## 7. Conclusion

The expected TCP/NTCP metrics, QALY score and secondary cancer risk estimations, are related to the DVH metric and radiobiological tools. Among other considerations, this should attract attention about the critical choice of radiobiological parameters setting and dose calculation algorithm to better estimate TCP/NTCP, otherwise important uncertainties can be expected. To date, only the MC method is considered the most accurate algorithm for dose calculation, but it requires the greatest processing time. Apart from MC method, all other algorithms make different degrees of approximation and simplification leading to less calculation time, but also resulting in less accurate dose distribution comparing with the MC simulation. The realistic approach, to choose and rank radiotherapy plans to make a clinical decision, need that the DVH should be calculated using the more accurate algorithm.

## Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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