International Journal of Cancer Therapy and Oncology
www.ijcto.org

Radiobiological assessment of dose-to-medium or dose-to-water with Acuros XB algorithm compared with Anisotropic Analytical Algorithm for lung cancer radiotherapy- What should we know to manage the transition?

Abdulhamid Chaikh[1,2,3*], Catherine Khamphan[4], Alexia Delbaere[4], Nicolas Docquiere[1], Jarkko Ojala[5], Robin Garcia[4], Juliette Thariat[3,6,7], Jacques Balosso[1,2,6,8]

[1]*Department of Radiation Oncology and Medical physics. University Hospital of Grenoble Alpes (CHUGA), France.*
[2]*France HADRON national research infrastructure, IPNL, Lyon, France.*
[3]*Laboratoire de physique corpusculaire IN2P3/ENSICAEN - UMR6534, France*
[4]*Department of Medical physics. Institut Sainte Catherine, Avignon, France.*
[5]*Department of Oncology & Department of Medical Physics, Tampere University Hospital (Tays), Tampere, Finland.*
[6]*Unicaen - Normandie Université, Caen, France.*
[7]*Department of Radiation Oncology. Centre François Baclesse.*
[8]*University Grenoble-Alpes – Grenoble- France.*

Received March 04, 2017; Revised October 20, 2017; Accepted November 22, 2017; Published Online December 15, 2017

Original Article

Abstract

Purpose: To track the dosimetric changes for similar dose prescriptions, when dose calculation algorithms are upgraded in the treatment planning system (TPS). Clinically significant representations of the treatment outcomes are used to provide interpretable data for radiation oncologists, as the equivalent uniform dose (EUD), the tumor control probability (TCP), the late toxicity as normal tissue complication probability (NTCP) and the uncomplicated tumor control probability (UTCP) scores. Results are presented and discussed in a clinical perspective. **Methods:** Ten lung cancer patients were included in this study. For each patient, five treatment plans were generated. The doses were calculated using Anisotropic Analytical Algorithm (AAA) and both Acuros XB (AXB) dose reporting modes: dose-to-medium AXB D(m,m) and dose-to-water AXB D(w,m). In plans 1, 2 and 3, the doses were calculated respectively with AAA, AXB D(m,m) and AXB D(w,m) using exactly the same prescription dose and beam set-up. The doses in plans 4 and 5 were calculated using both AXB dose reporting modes using, as input, the same number of monitor units (MUs) as yielded by AAA, with the same beam set-up. The EUD, TCP and NTCP were computed using the assumed radiobiological parameters from literature. The Wilcoxon paired test was used to calculate p-values. **Results:** Using the same prescription dose, TCP values were higher with AXB than with AAA, and corresponding UTCP scores were 1-2% better with $p < 0.05$. In addition, absolute NTCP values were slightly increased with AXB. Both AXB dose reporting modes yielded comparable lower TCP and NTCP values (again in the order of 1-2%) than with AAA, when using same MU numbers as with AAA. **Conclusion:** Compared to AAA, taken as reference, both AXB dose reporting modes yielded better results. AAA showed very close values to AXB D(w,m), but it is difficult to give recommendation between D(w,m) and D(m,m) yet, due to the lack of recommended radiobiological parameters associated with these dose reporting modes. We suggest doing experimental and modelling studies to determine the real radiobiological effects in both targets and organs at risks. Should the differences be substantial in some conditions and relevant to clinical practice, discussions

***Corresponding author**: Abdulhamid Chaikh; Department of Radiation Oncology and Medical Physics, University Hospital of Grenoble Alpes (CHUGA), Grenoble, France.

***Cite this article as**: Chaikh A, Khamphan C, Delbaere A, Docquiere N, Ojala J, Garcia R, Thariat J, Balosso J. Radiobiological assessment of dose-to-medium or dose-to-water with Acuros XB algorithm compared with Anisotropic Analytical Algorithm for lung cancer radiotherapy- What should we know to manage the transition?. Int J Cancer Ther Oncol. 2017; 5(1):5118. **DOI:** 10.14319/ijcto.51.8*

ISSN 2330-4049

regarding dose prescription and optimization of the tolerance doses to OAR should be undertaken between medical physicists and radiation oncologists.

Keywords: Acuros XB, TCP, NTCP, UTCP.

1. Introduction

Different dose calculation algorithms result in variable dose distributions that may be relevant to patients. Moreover, the most recent algorithms, having improved accuracy, often result in more dose heterogeneity influencing radiotherapy efficacy and safety, for both tumors and normal tissues, respectively. Algorithms, such as Analytical Anisotropic Algorithm (AAA)[1-4] and recent Acuros XB algorithm (AXB), both implemented in Eclipse™ treatment planning system (TPS) (Varian Medical Systems, Inc., Palo Alto, CA), are close to, or based on, Monte Carlo methods. AXB has two dose reporting modes: dose-to-water in medium (D(w,m)) or dose-to-medium in medium (D(m,m)). Historically, dose calculation algorithms were based on the dose-to-water assuming an homogeneous water target (D(w,w)). Then, the D(w,m) was introduced in conventional radiotherapy to take into account heterogeneities, such as lung and bone. Thus, the clinical validation of the D(m,m) mode may be an issue because the reference for clinical data are based on D(w,w). The question regarding the extent of the dose prescription adjustments has been brought out for some years, when the transition from algorithms of type (A) to type (B) were carried out[5,6]. Discussions and recommendations based on dosimetric, statistical and radiobiological criteria to ensure a safe transition have been published[5,6].

In this context, 3D conformal radiation therapy (3DCRT) is a convenient technique to evaluate the real impact of a change of the dose calculation algorithm[7]. 3DCRT allows the use of a minimal number of technical parameters, conversely to more complicated techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated radiotherapy (VMAT) or stereotactic body radiotherapy (SBRT). The latter is particularly challenging due to small fields and electronic disequilibrium. Thus, we used 3DCRT plan evaluations that could be performed with straightforward physical parameters derived from dose volume histograms (DVH).

At present, radiobiological modelling can be used to compare and rank radiotherapy plans as well as to perform *in silico* prediction of clinical outcomes such as tumor control probability (TCP) and normal tissue complication probability (NTCP). In addition, multiple parameters can be integrated into one more clinically relevant score, such as: the uncomplicated tumor control probability (UTCP)[8], which represents tumor control probability in the absence of treatment-related complications. The UTCP score was recently proposed for the estimation of the quality of life (Qol), thereby providing the most integrated information by taking into account radiation-induced side effects and their consequences on the wellbeing of an individual for a given cancer site[9]. UTCP aims to be a sensitive score of the global clinical impact resulting from a change of dose calculation algorithm. It should be evaluated with caution with respect to the radiobiological models and parameters used.

To the best of our knowledge, no previous study has been published on lung cancer treatment plans using the UTCP to evaluate the potential impact of AXB dose reporting modes on clinical radiotherapy outcomes, compared to AAA taken as reference. In this study, we raise two questions: firstly, what should we know regarding dose prescription adjustment, when moving from AAA to AXB? Secondly, what should one be aware of when considering radiobiological assessment for D(m,m) or D(w,m)?

Thus, the primary aim of this study is to highlight the differences in real delivered dose from DVH translated into equivalent uniform dose (EUD) for lung radiotherapy treatment plans. The secondary aim is to compare TCP, NTCP and UTCP scores between plans that exhibit differences in dose distributions. It is hypothesized that UTCP scores could predict the global Qol and could be used as a clinical indicator to safely move from AAA to AXB.

2. Methods and Materials

2.1. Dose calculation models

The dose calculations were performed using AAA and AXB with both dose reporting modes. The algorithms were integrated in version 13.5 of Varian Eclipse™ TPS. In both algorithms, heterogeneity corrections are performed. In AAA, three sub-sources are modeled, including primary photons, extra-focal photons and electron contamination. AXB uses a sophisticated technique to solve the Linear Boltzmann transport equation (LBTE) and it directly accounts for the effects of heterogeneities in patient dose calculations[10-16].

2.2. Clinical cases and treatment planning

Ten patients with lung cancer were included in this study. Radiation oncologists delineated the target structures and organs at risk (OARs). The total dose prescribed to the planning target volume (PTV) was 54

to 66 Gy with a daily dose of 1.8 or 2 Gy to be treated in 30 or 33 fractions. The prescription was done on the 95% isodose that encompassed the whole PTV. The dose constraints to the OARs are based on the international recommendations. Two methods were used to compare the treatment plans[7]:

- **Method 1:** this method requires a fixed prescription dose and normalization with identical beam arrangements. For this objective, for each patient a set of three plans was generated using AAA, AXB D(m,m) and AXB D(w,m).
- **Method 2:** this method requires a fixed number of monitor units (MUs) and normalization obtained from AAA to re-calculate the dose distribution with AXB. For this objective, plans 4 and 5 were generated. Dose distributions were re-calculated with AXB D(m,m) and AXB D(w,m) using the number of MUs obtained from AAA as input and the same beam arrangements. Thus, reliable plan comparisons were performed to assess the effect of dose calculation for each field.

The Figure 1 shows the method used to compare radiotherapy plans.

2.3. Radiobiological modeling

2.3.1. Equivalent uniform dose

Cumulative DVHs were calculated for all plans, and then converted into differential DVH. The EUD model proposed by Niemierko 1997, was used to calculate the TCP and NTCP[17,18]. According to Niemierko's model, EUD is defined as:

$$EUD = \left(\sum_i v_i LQED_i^a \right)^{1/a} \quad (1)$$

where (v_i) is the fractional organ volume receiving a dose (D_i) and (a) is a tissue specific parameter that describes the volume effect. For a=1, the power law-based EUD becomes the arithmetic mean dose, typical for parallel organs. When a < 1, it weighs more on the low dose region, typical for target volumes. In contrast, when a > 1, it weighs more on the high-dose region, typical for serial organs.

To account for variations in dose per fraction in different subvolumes of target or OARs, with changes in fractionation schedules, total physical dose corresponding to each DVH bin, D_i, was converted into biological equivalent physical dose of 2 Gy fractions using linear quadratic (LQ) model[19]:

$$LQEDi = D_i \frac{1 + \frac{D_i / nf}{\alpha / \beta}}{1 + \frac{2}{\alpha / \beta}} \quad (2)$$

where (nf) is the number of fractions. The α/β is the tissue-specific LQ parameter taken from QUantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) recommendations[20,21,22].

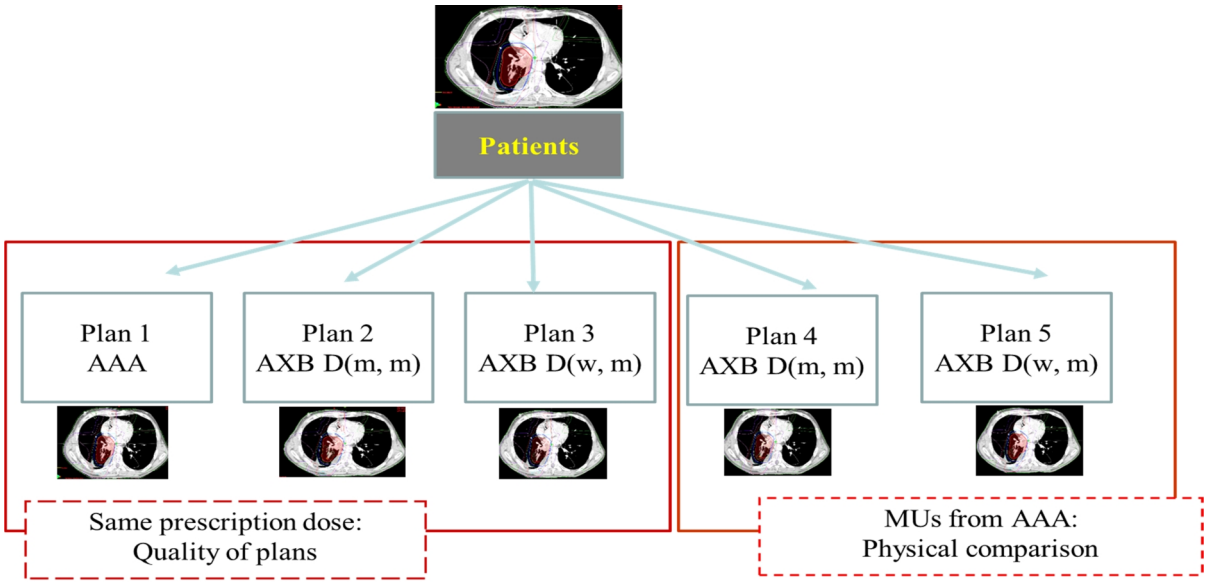

Figure 1: The two normalization methods (prescription dose, left panel; and the MU numbers, right panel) used to compare lung radiotherapy plans with 3DCRT.

Table 1: Radiobiological parameters for TCP and NTCP for selected OARs in this study.

Structures	Endpoint	TCD_{50}/TD_{50} [Gy]	α/β	a	γ_{50}
PTV	Tumor control	TCD_{50} = 51.24	10.0	-10.0	0.83
Lung-PTV	Pneumonitis	TD_{50} = 29.14	4.0[20]	1.0	2.0
Heart	Pericarditis	TD_{50} = 48.0	2.5[21]	3.1	3.0
Esophagus	Clinical stricture/ perforation	TD_{50} = 68.0	10.0[22]	18.0	4.0

2.3.2. Tumor control probability

Niemierko's EUD-based TCP is defined as:

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

where TCD_{50} is the dose to control 50% of the tumors, when the tumors are homogeneously irradiated. The factor (γ_{50}) describes the slope of the dose-response curve. The parameters for TCD_{50} and γ_{50} for target were taken from Okunieff *et al.* considering macroscopic tumor[23]. For lung tumors: α/β = 10 Gy and a = -10 were selected for this study.

2.3.3. Normal tissue complication probability

Niemierko's EUD based NTCP is defined as:

$$NTCP = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{4\gamma 50}} \qquad (4)$$

where TD_{50} is the tolerance dose for 50% complication rate of the normal organ. TD_{50} for lung was taken from Hedin E *et al.* 2013, where the parameter was well-adapted for AAA algorithm[24] For the heart and esophagus, the TD_{50} were taken from Emami–Burman parameters[25]. The value of TD_{50} for each organ also reflects the level of toxicity to be modelled. The values of parameters (γ_{50}) and (a) [in EUD] were taken from Niemierko's model. Table 1 shows the radiobiological parameters for target and OARs considered in this study[26,27].

2.3.4. Uncomplicated tumor control probability

In order to quantify the benefit and toxicity balance of the treatment for a given patient, the UTCP is calculated as[28]:

$$UTCP = TCP * (1 - \prod_{i=1}^{3} NTCP) \qquad (5)$$

where (i) = 3 according to the three OARs, including healthy lung, heart and esophagus.

2.4. Statistical analysis

The same CT scan for each patient was used to generate 5 different treatment plans. Then, the dose was recalculated with AAA and both AXB dose reporting modes. Thus, there was a relationship for each patient between the dosimetric data from reference plan, AAA, and the tested plans with both AXB dose reporting modes. In this case, different sets of dosimetric data are used as input to estimate EUD, TCP, NTCP and UTCP for a given patient. Thus, the Wilcoxon signed rank test was used to calculate the p-value, considering $p < 0.05$ as a significance difference[29]. The null hypothesis means that radiobiological indices in all plans do not significantly differ from 0. In addition, the statistical correlation between predicted radiobiological indices obtained from AXB with both dose reporting modes, and with AAA, was evaluated using Spearman's correlation coefficient (ρ-value).

3. Results

3.1. Tumor control probability

The EUD values in plans 2 and 3 using AXB D(m,m) and AXB D(w,m) were increased. They predicted more dose to the target compared with AAA, on average 0.4% (1.6 SD) and 0.1% (1.2 SD), respectively. Thus, TCP values in plans 2 and 3 were also increased, on average by 0.8% (2.2 SD) and 0.4% (1.4 SD), respectively, as TCP depends on EUD. The data did not show any significant difference, when comparing AAA with both AXB dose reporting modes, with $p > 0.05$. In addition, the data showed a strong correlation for both AXB dose reporting modes vs. AAA, with $\rho > 0.85$. Plans 4 and 5 were more realistic for the comparison of both algorithms. Using the same MUs as with AAA as input, EUD as well as TCP values were lower than with AAA by 1.0 % (1.3 SD) and 0.2 % (1.5 SD) using AXB D(m,m) and AXB D(w,m), respectively. The Wilcoxon test indicated no significant difference between TCP calculated from AAA with both AXB dose reporting modes. In addition, the data showed a strong correlation for both AXB dose reporting modes vs. AAA, with $\rho > 0.98$.

Figure 2 shows the average values for EUD and TCP from all plans using AAA and both AXB dose reporting modes. It can be seen, compared with AAA, that the AXB shows larger EUD values leading to larger TCP. Conversely, the average TCP values in plans 4 and 5 using the same MU as with AAA were slightly lower compared to AAA. However, to conclude about which is the better plan, one should consider the most accurate algorithm being AXB. Using the same MUs as with AAA to recalculate DVH with AXB, in the present study, AAA certainly overestimates the TCP value by 1-2%.

 ISSN 2330-4049

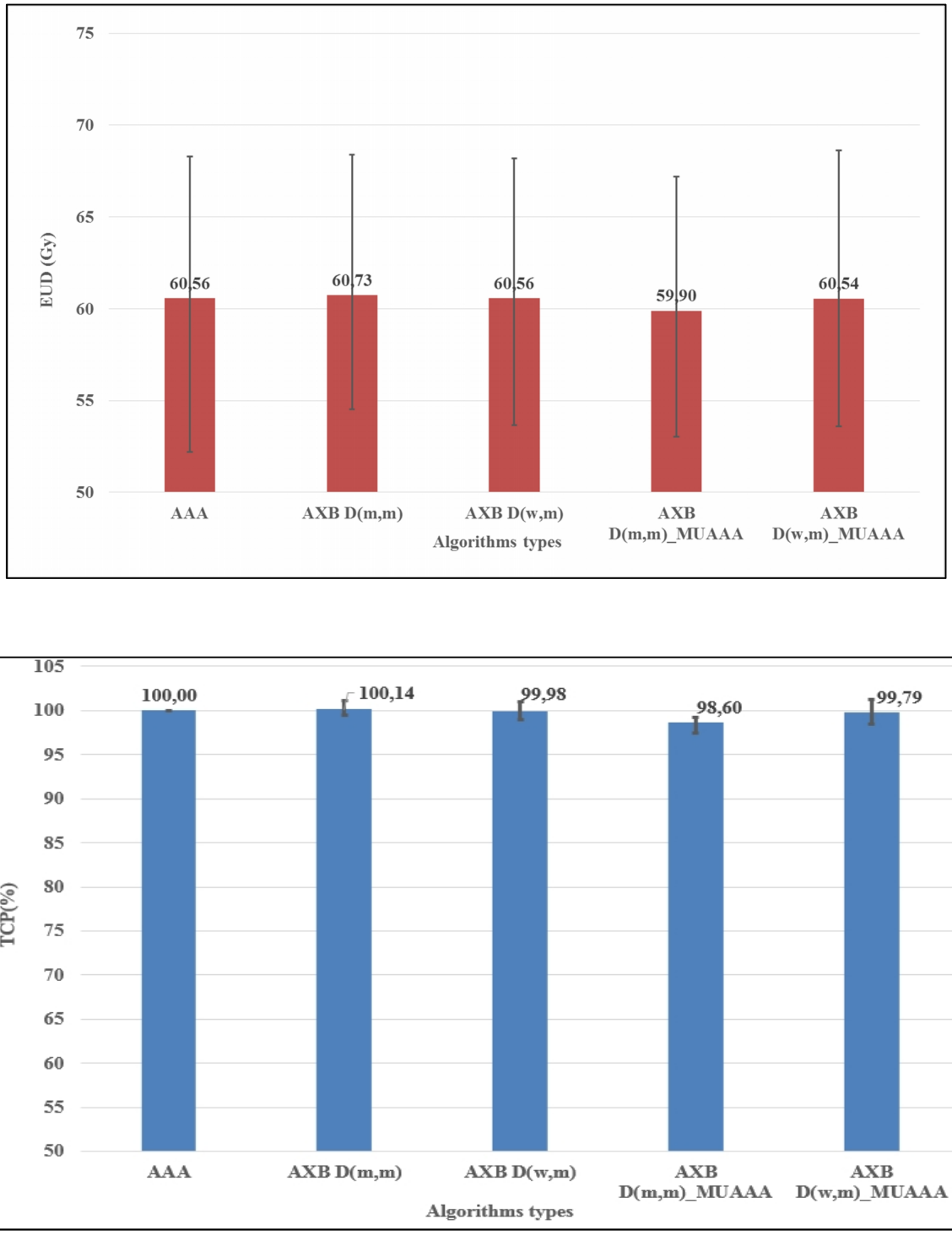

Figure 2: The average values for EUD (upper panel) and TCP (lower panel) from all lung cancer treatment plans, created using a 3DCRT technique with AAA and both AXB dose reporting modes. The TCP values were normalized to 100% *vs.* AAA considered as the reference, to better estimate the shift in TCP values.

Table 2: The average values for EUD and NTCP from all plans as well as p-values for NTCP. The doses in plans 1, 2 and 3 were calculated, respectively with AAA and both AXB dose reporting modes using the same prescription dose. The doses in plan 4 and 5 were calculated with AXB using MUs from AAA.

		AAA Plan 1	AXB D(m,m) Plan 2	AXB D(w,m) Plan 3	AXB D(m,m) Plan 4	AXB D(w,m) Plan 5
Lung	EUD Gy	10.7[2.1;13.5]	10.9[2.1;13.7]	10.8[2.1;13.7]	10.7[2.0;13.4]	10.7[2.0;13.4]
	NTCP %	0.08[0.0;0.21]	0.1[0.0;0.24]	0.1[0.0;0.23]	0.08[0.0; 0,2]	0.08[0.0;0.2]
	p-values	-	0.004	0.2	0.37	0.01
Heart	EUD Gy	20.5[0.3;32.5]	20.4[0.3;33.5]	20.6[0.3;33.8]	20.1[0.3;32.7]	20.6[0.3;33.3]
	NTCP %	0.25[0.0;0.9]	0.27[0.0;1.3]	0.3[0.0;1.4]	0.3[0.0;1.4]	0.3[0.0;1.2]
	p-values		0.2	0.8	0.08	0.6
Esophagus	EUD Gy	53.9[44.4;58.6]	53.6[44.0;58.0]	53.9[44.7;58.1]	52.9[43.6;57.5]	53.8[44.7;58.5]
	NTCP %	3.7[0.1;8.5]	3.3[0.1;7.3]	3.6[0.1;7.4]	2.8[0.1;6.4]	3.6[0.1;8.4]
	p-values	-	0.06	0.04	0.002	0.002

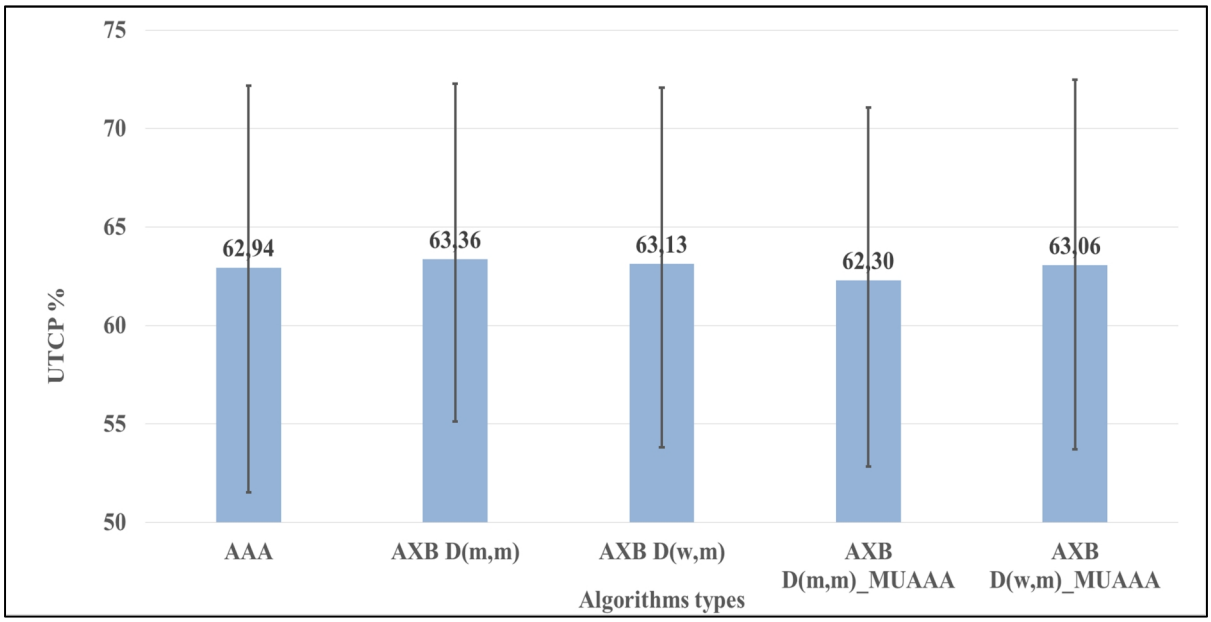

Figure 3: UTCP with average values from AAA and both AXB modes for lung cancer treatment plans, created by 3DCRT technique.

3.2. Normal tissue complication probability

The EUD values in plans 2 and 3 using both AXB dose reporting modes were increased for healthy lung. They predicted larger NTCP compared with AAA. Table 2 shows the average values for EUD and NTCP from all plans. It can be seen that the NTCP from plans 4 and 5 were close to AAA. Using the same MUs from AAA to re-calculate the DVH with both AXB dose reporting modes, it showed much similar NTCP values.

3.3. Uncomplicated tumor control probability

Figure 3 shows the UTCP with average values from all series of plans. The data showed no significant difference, when comparing AAA with AXB, with $p > 0.05$. In addition, the data showed a strong correlation for both AXB modes vs. AAA, with $\rho = 0.99$.

4. Discussion

In this radiobiological evaluation, we compared two dose calculation algorithms (AXB *vs.* AAA) that were used to calculate dose distributions in lung cancer treatment plans, created using a 3DCRT technique. In this study, both AXB dose reporting modes and AAA demonstrated comparable TCP values within 1-2%, using the same prescription dose. Our results are consistent with those found by Liang *et al*. 2016, for IMRT[30]. However, the difference between the results of AXB and AAA may become clinically less significant using the same MUs as with AAA. The use of AXB D(w,m) that considers water equivalence for the voxel dose calculation, the results were very similar. Thus, the choice of the AXB dose reporting mode plays some role: firstly in the calculation of the delivered dose in MUs as standard indicator to compare dose calculation

algorithms[31] and secondly, the delivered dose will influence radiotherapy outcomes. The advantage of 3DCRT, as a reference technique, is to compare the new algorithm without introducing many parameters influencing the results. In this context, it is interesting to note that the impact of dose calculation may differ depending on treatment delivery techniques, beam orientation and prescription dose method. Thus, it is essential to further investigate the output of both AXB dose reporting modes, for any treatment delivery techniques, to measure or estimate more accurately the dose modifications. The objective is to avoid the over/under irradiation of the patients, which could translate into variations of TCP, NTCP and UTCP. The risk of over irradiation is likely to increase the normal tissue toxicities, NTCP, while under coverage would increase the risk of local recurrence.

4.1. Medical decision: D(m,m) or D(w,m) *vs.* AAA

The choice of the dose reporting modes is a critical issue, because dose distribution is the basic information for all radiobiological models. However, moving from AAA to AXB D(w,m), *using 3DCRT*, would most probably produce similar results regarding treatment plan quality or UTCP as a surrogate parameter, assuming that the radiobiological parameters are well-adapted. Thus, AXB D(w,m) algorithm could be validated for clinical use. In addition, full MC simulations are encouraged as a verification method for some situations with heterogeneous media such as lung, bone and high-Z materials[32]. However, the implementation of D(m,m) needs more relevant radiobiological data to refine and confirm the predicted TCP and NTCP. The cohort used in this study is small (n = 10). However, this is the first study proposing a radiobiological approach for the choice between D(m,m) and D(w,m). Thus, we suggest doing several studies using the approach proposed in this study to determine the effect on dose distributions for both targets and OARs for various anatomical regions. If substantial differences would be discovered, a discussion regarding the dose prescription and the tolerance doses should take place among physicists and oncologists about the need to adjust or not the prescriptions, as well as, to optimize the OARs protection, to keep on with the same clinical results.

4.2. Caution with radiobiological parameters

Early radiation-induced toxicity during the radiotherapy course can be observed and may result in treatment interruption and protraction. However, it is a very different biological process than delayed toxicity and radiobiological models have to be specifically tuned for early or late NTCP and adapted to the level of severity (grade 1 to 4). For example, acute esophagitis is observed in a large proportion of patients treated for lung cancer while NTCP model estimates late toxicity rates of about 3% (Table 2)[33,34].

For delayed, or late toxicity, the probability and the severity of toxicity depend on the delivered dose to the OAR itself. The delivered dose could be translated into a EUD value using differential DVH. Thus, increasing EUD could increase NTCP and severity of toxicities. In this study, we simulated the dose-effect relationship probability using the NTCP model that integrates the EUD concept. Historically the NTCP models were tuned with high TD_{50}, to predict for severe toxicity and thus to avoid dangerous or disabling damages to the patients. Available parameters, listed in Table 1, were used, assuming they are adapted for this comparison, i.e. to severe late effects; although we could not find in the literature the radiobiological parameters adapted to AXB D(m,m).

Only a few studies in the literature evaluated the TD_{50} for NTCP for lung according to algorithms of types (A) or (B)[24]. Thus, it is relevant to mention that previous radiobiological modeling studies for lung cancer, applying EUD or Lyman-Kutcher-Burman (LKB) approach, have used TD_{50} = 24 Gy, without heterogeneity correction. More recently, this value was re-estimated for AAA[35], yielding a higher value fully consistent with the underestimation of the real dose by the former algorithms of type (A). This is a critical issue, since using TD_{50} = 24 Gy instead of 29.14 Gy, would increase the NTCP in absolute value. Since we do not have sufficient clinical data to ascertain a refined absolute estimation of NTCP, it is better, presently, to use ΔNTCP. However, if the comparison is based on EUD and considering that, the increase of EUD would increase the NTCP, we can confirm that the application of the same prescription dose, when moving from AAA to AXB would increase EUD for lung, heart and esophagus.

In this study to make a reliable estimation, the radiobiological parameters for OARs were taken from LKB[35,36], as well as TD_{50} assumed for AAA for lung was used. It should be clear that, using more adapted radiobiological parameters is the optimal approach to compare, *in silico*, the radiotherapy outcomes, when a new algorithm is implemented. In this regard, it is important to note that there are some limitations that may influence the interpretation of the predicted results. Firstly, the comparison is based on patients really treated with AAA and virtually planned with AXB. Thus, we used the same cohort, but in reality, the cohort would be different at the time of real clinical use of AXB. Secondly, there are studies showing that the relationship between dose distribution parameters and side effects might differ among different patient populations[37,38]. It cannot be excluded that the patient anatomy and lung density would influence the dose distribution and thus, would indirectly influence the radiotherapy outcome predictions and a small population may not be representative of these hypothetic conditions.

5. Conclusion

We compared TCP and NTCP from AAA and both AXB dose reporting modes using radiobiological parameters from literature. As a whole, the step from AAA to AXB is much smaller than the step between type (A) to type (B) algorithms. In this instance, the change from type (A) directly to type (C), non-MC or MC algorithm would be dangerous without a similar study, as reported in this paper[39]. However, a large cohort with cumulated data is needed to reduce the uncertainties in the assumptions used to predict TCP and NTCP, as well as to improve the calibration of the radiobiological models. The use of radiobiological parameters assumed from clinical experience derived from D(w,m) to estimate TCP and NTCP with D(m,m) would produce uncertainty regarding the clinical outcomes.

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.

Funding

This research was supported in part by ProtonShare project, the French research funding agency, Agence Nationale de la Recherche, in the frame of the "Investments for the Future" under the reference: France HADRON, ANR-11-INBS-0007.

References

1. Sievinen J, Ulmer W, Kaissl W. AAA photon dose calculation model in Eclipse. Palo Alto (CA). Varian Medical Systems; 2005:1–18.
2. Ojala JJ, Kapanen MK, Hyödynmaa SJ *et al*. Performance of dose calculation algorithms from three generations in lung SBRT: comparison with full Monte Carlo-based dose distributions. Journal of applied clinical medical physics.2014;15(2):4-18.
3. Failla GA, Wareing T, Archambault Y, *et al*. Acuros XB advanced dose calculation for the Eclipse treat¬ment planning system. Clinical Perspectives. 2010.
4. Rana S. Clinical dosimetric impact of Acuros XB and analytical anisotropic algorithm (AAA) on real lung cancer treatment plans: review. Int J Cancer Ther Oncol. 2014;2:02019.
5. Xiao Y, Papiez L, Paulus R *et al*. Dosimetric Evaluation of Heterogeneity Corrections for RTOG 0236: Stereotactic Body Radiation Therapy of Inoperable Stage I/II Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2009; 73(4):1235–42.
6. Chaikh A, Balosso J. Should the dose prescription be readjusted when using tissues density corrections algorithms for radiation oncology ? J Case Rep Onc Ther. 2014; 1(1):01018.
7. Chaikh A, Giraud JY, Balosso J. A method to quantify and assess the dosimetric and clinical impact resulting from the heterogeneity correction in radiotherapy for lung cancer. Int J Cancer Ther Oncol. 2014;2(1):020110.
8. Agren A, Brahme A, Turesson I. Optimization of uncomplicated control for head and neck tumors. Int J Radiat Oncol Biol Phys. 1990;19:1077-85.
9. Chaikh A, Docquière N, Bondiau PY, *et al*. Impact of dose calculation models on radiotherapy outcomes and quality adjusted life years for lung cancer treatment: do we need to measure radiotherapy outcomes to tune the radiobiological parameters of a normal tissue complication probability model? Transl Lung Cancer Res. 2016;5(6):673-80.3.
10. Vassiliev ON, Wareing TA, McGhee J, *et al*. Validation of a new grid-based Boltzmann equation solver for dose calculation in radiotherapy with photon beams. Phys Med Biol. 2010;55(3):581–98.
11. Ulmer W, Harder D. A triple Gaussian pencil beam model for photon beam treatment planning. Z Med Phys. 1995;5(1):25–30.
12. Ulmer W, Harder D. Applications of a triple Gaussian pencil beam model for photon beam treatment planning. Z Med Phys. 1996;6(2):68–74.
13. Ulmer W, Kaissl W. The inverse problem of a Gaussian convolution and its application to the finite size of the measurement chambers/detectors in photon and proton dosimetry. Phys Med Biol. 2003;48(6):707–27.
14. Ulmer W, Pyyry J, Kaissl W. A 3D photon superposition/convolution algorithm and its foundation on results of Monte Carlo calculations. Phys Med Biol. 2005;50(8):1767–90.
15. Tillikainen L, Siljamäki S, Helminen H, *et al*. Determination of parameters for a multiple-source model of megavoltage photon beams using optimization methods. Phys Med Biol. 2007;52(5):1441–67.
16. Tillikainen L, Helminen H, Torsti T *et al*. A 3D pencil-beam-based superposition algorithm for photon dose calculation in heterogeneous media. Phys Med Biol. 2008;53(14):3821–39.
17. Niemierko A. Reporting and analyzing dose distributions: A concept of equivalent uniform dose. Med Phys 1997;24(1):103–10.
18. Gay HA, Niemierko A. A free program for calculating EUD-based NTCP and TCP in

external beam radiotherapy. Physica Medica 2007;23:115-25.
19. Allen Li X, Alber M, Deasy OJ *et al*. The use and QA of biologically related models for treatment planning: Short. Med. Phys. 2012;39 (3):1386-409
20. Marks LB, Bentzen SM, Deasy JO *et al*. Radiation dose–volume effects in the lung. Int. J. Radiation Oncology Biol. Phys. 2010;76(3):S70–S76.
21. Gagliardi G, Constine LS, Moiseenko V *et al*. Radiation dose–volume effects in the heart. Int. J. Radiation Oncology Biol. Phys. 2010; 76(3):S77–S85.
22. Wasik MW, Yorke E, Deasy J, et al. Radiation dose-volume effects in the esophagus. Int. J. Radiation Oncology Biol. Phys.2010;3(76):S86–S93.
23. Okunieff P, Morgan D, Niemierko A, *et al*. Radiation dose-response of human tumors. Inr. J. Radiation Oncology Biol. Phys. 1995;4(32): 1227-37.
24. Hedin E, Bäck A. Influence of different dose calculation algorithms on the estimate of NTCP for lung complications. Journal of applied clinical medical physics. 2013;14(5):127-39.
25. Burman C, Kutcher GJ, Emami B, *et al*. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys. 1991;21:123–35.
26. Niemierko A. Biological optimization. In: Bortfeld T, Schmidt-Ullrich R, De Neve W, Wazer DE, editors. Image-guided IMRT. Berlin: Springer-Verlag; 2006:199–216.
27. Gay HA, Niemierko A. A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy. Physica Medica. 2007;23:115-25.
28. Chaikh A, Balosso J. A decision protocol to propose proton versus photon radiotherapy: in silico comparison. Radiotherapy and oncology, 2016;119(1),EP-2077: S979.
29. Chaikh A, Giraud JY, Perrin E, *et al*. The choice of statistical methods for comparisons of dosimetric data in radiotherapy. Radiation oncology. 2014;9:205.
30. Liang X, Penagaricano J, Zheng D. Radiobiological impact of dose calculation algorithms on biologically optimized IMRT lung stereotactic body radiation therapy plans. Radiation Oncology. 2016;11:10.
31. Chaikh A, Balosso J. 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? Transl Lung Cancer Res 2016;5(6):681-7.
32. Ojala J. The accuracy of the Acuros XB algorithm in external beam radiotherapy – a comprehensive review. Int J Cancer Ther Oncol. 2014;2(4):020417.
33. Caglar HB, Othus M, Allen MA. Esophagus in-field: A new predictor for esophagitis. Radiotherapy and Oncology.2010;97:48–53.
34. Belderbos J, Heemsbergen W, Hoogeman M, *et al.* Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. Radiotherapy and Oncology. 2005;75:157–64.
35. Lyman JT. Complication probability as assessed from dose volume histograms. Radiat Res Suppl. 1985;8:S13–S19.
36. Kutcher GJ, Burman C, Brewster L, *et al*. Histogram reduction method for calculating complication probabilities for three dimensional treatment planning evaluations. Int J Radiat Oncol Biol Phys. 1991;21:137–46.
37. Peeters ST, Hoogeman MS, Heemsbergen WD, *et al*. Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: normal tissue complication probability modeling. Int J Radiat Oncol Biol Phys. 2006;66:11–9.
38. Langendijk JA, Lambin P, Ruysscher D, *et al*. Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach. Radiotherapy and Oncology. 2013;107:267–73.
39. Chaikh A, Khamphan C, Kumar T, *et al*. What should we know about photon dose calculation algorithms used for radiotherapy? Their impact on dose distribution and medical decisions based on TCP/NTCP. Int J Cancer Ther Oncol. 2016;4(4):4418.

 ISSN 2330-4049