Acta Oncologica, 2014; 53: 324–329

informa
healthcare

ORIGINAL ARTICLE

Clinical impact of using the deterministic patient dose calculation algorithm Acuros XB for lung stereotactic body radiation therapy

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Abstract

Purpose. To evaluate the clinical impact of using the deterministic dose calculation algorithm, Acuros XB, for early stage lung cancer patients undergoing stereotactic body radiotherapy (SBRT). *Material and methods.* Seventy-seven stage I non-small cell lung cancer patients who underwent lung SBRT from 2008 to 2012 at our center were included in this study. All treatment plans originally calculated by the anisotropic analytical algorithm (AAA) were recalculated using the AAA and Acuros XB algorithms with identical monitor units and beam arrangements. The dose, dose distribution, conformality number (CN) and heterogeneity index (HI) of the target were determined for each plan. A paired matched t-test was used to evaluate the difference between the mean dose, the dose distribution, and the CN and HI for the target. The importance of tumor (volume, location), patient (pulmonary functional, body mass index) and treatment (number of SBRT beams) on the dose distributions obtained from the two algorithms was statistically determined using linear regression analyses. *Results.* The mean target dose was same for both algorithms. Compared to AAA, a small and significant difference in dose distribution in the target was found for the Acuros XB algorithm, resulting in lower conformity (-2.1%, $p < 0.0001$) and higher heterogeneity ($p < 0.0001$) of dose. Single logistic regression identified pulmonary function, number of beams and target location as being correlated with the difference of CN between the two calculations. Multivariate analysis indicated that the patient's pulmonary function ($p = 0.0296$) was the only predictor for the difference in conformality between the two dose calculation algorithms. *Conclusions.* In lung SBRT, the patient's pulmonary function is responsible for the difference in target dose distribution between the Acuros XB and AAA algorithms. The Acuros XB algorithm could be used to advantage in patients with compromised pulmonary function based on its accurate modeling of lung tissue in comparison to AAA.

Stereotactic body radiation therapy (SBRT) is an effective treatment for early stage non-small cell lung cancer (NSCLC) patients who are medically inoperable or decline surgery [1]. SBRT utilizes multiple beams to yield a highly conformal dose distribution with rapid falloff at the periphery of the target, resulting in reduced toxicity to the healthy surrounding tissues. As there is a significant correlation between tumor local control and the delivered dose of SBRT [2–4], applying an accurate and highly conformal dose to the target is of critical importance.

Recently, the latest version of the Eclipse treatment planning system has released the Acuros XB algorithm for clinical use (Varian Medical Systems, Palo Alto, CA, USA). Acuros XB distinguishes itself from the other clinical convolution-based algorithms in that it provides a deterministic solution to the Linearized Boltzman Transport equation [5]. This approach requires the macroscopic cross-section of the actual material within which radiation transport is considered. Therefore, all of the voxels of the CT image in a patient have to be categorized in terms of known biological tissues such as lung, soft tissue, bone, etc. This novel feature of the dose calculation results in dose to the actual heterogeneous tissue, a feature only shared by the Monte Carlo (MC) based algorithm [6,7]. There have been a number of studies published on

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(Received 8 May 2013; accepted 27 June 2013)

ISSN 0284-186X print/ISSN 1651-226X online © 2014 Informa Healthcare
DOI: 10.3109/0284186X.2013.822552

benchmarking the Acuros XB dose calculation against MC solutions [5,8–11]. Being amongst the most heterogeneous of thoracic tissues, lung can benefit significantly from improved dose calculations [12]. The currently widely utilized Anisotropic Analytical Algorithm (AAA) is known to overestimate dose at the air-tumor interface and underestimate dose at the bone-tumor interface [13,14]. For 4–6 MV beams and field sizes $\geq 5 \times 5$ cm^2, AAA tends to underestimate the dose in lung and overestimate the dose in water-equivalent tissue after the lung. For 6 MV, the errors are reported to be smaller than 3% of the maximum dose on the central axis (Dmax). However, the fractional error in local dose can become significantly larger, if the local dose is small relative to Dmax [15,16].

Lung is a complex heterogeneous medium in which the high density target is surrounded by low density lung tissue; or, occasionally, the tumor is partially bounded by high density tissue such as chest wall or ribs. The central zone of the lung has a slightly higher density than the peripheral lung [17]. An emphysematous lung, which is common in such patients, has an even lower density in comparison to normal lung due to the destruction of alveoli, which merge into bulla (large air cysts) [18]. These intrinsic factors can lead to inaccuracies with the current dose calculation algorithms. The availability of a more accurate algorithm, the Acuros XB, can be expected to lead to more accurate dose calculations [5,8,9,19].

The aim of the current study is to examine the clinical impact of using the Acuros XB dose calculation algorithm in lung SBRT. We hypothesize that: 1) the tumor volume and its anatomic location inside lung tissue; 2) the patients' pulmonary function and body mass index (BMI) status; and 3) the number of beams used in SBRT will all influence the difference in target dose distributions calculated by Acuros XB and AAA.

Material and methods

Patients selection

Seventy-seven patients who underwent lung SBRT between 2008 and 2012 at our Cancer Center were included in this study. All patients had early stage lung cancer that was either medically inoperable or the patient had voluntarily declined surgery. The regimen of 48 Gy in 4 fractions was used for peripheral tumors; whereas 60 Gy in 10 fractions was used for centrally located tumors, or for peripheral tumors whose planning target volume (PTV) was close to organs at risk (OARs), such as the mediastinum or the diaphragm. Targets were anatomically classified as central or peripheral depending on whether or not they were within 2 cm of the mediastinum or bronchial tree [20]. The patient's pulmonary function (FEV1) and BMI prior to radiotherapy were collected for data analysis. The study was approved by the university conjoint health research ethics board. Table I presents all relevant study-related parameters.

Table I. General information (n = 77).

Factors	Median (range) or cases
GTV (cm^3)	6.43 (0.5–78.01)
ITV (cm^3)	9.72 (1.05–104.12)
PTV (cm^3)	66.48 (19.01–372.43)
FEV1 (liter)	1.51 (0.45–2.92)
Number of beams	
6	14
7	48
8	5
9	10
Body mass index	27.05 (17.27–44.02)
Tumor location	
central vs. peripheral	14:63

GTV, gross target volume; ITV, internal target volume; PTV, planning target volume; FEV1, volume of air exhaled in the first second.

Simulation and target delineation

All patients were scanned in the supine position with a Brilliance Big Bore CT scanner (Philips Healthcare, Andover, MA, USA). Four-dimensional computed tomography (4D CT) data was acquired in 10 respiratory phase bins. The gross tumor volume (GTV) was defined on the exhale phase of the 4D CT, and the internal target volume (ITV) was generated using all 10 phases of the 4D CT scan in the ARIA Eclipse environment, Version 11 (Varian Medical Systems). The PTV was created by adding a 10 mm symmetric margin around the ITV.

Dose calculation and planning

All patient data were imported into the ARIA 11 environment. Acuros XB had been previously validated using homogeneous and heterogeneous calculations on a phantom. All treatment plans originally calculated by AAA, and approved for clinical use, were recalculated using the AAA and Acuros XB algorithms (version 11.0.21) with identical monitor units and beam arrangements. For the Acuros XB algorithm, the physics material table version 11.0 was used. This table is a physical material mapping to the various ranges of HUs encountered in a planning CT scan of the patient. "Field dose calculations" were performed for the Acuros XB, while the dose was reported as dose to the medium. For field dose calculations, the individual field doses are

calculated in separate Acuros XB runs. This option is useful for modification of field weights without the need to re-calculate the plan with Acuros XB. For AAA, the heterogeneous calculations were performed and the dose was reported as dose to water.

Dosimetric parameters evaluation

For the two algorithms, the mean dose to the PTV, the target dose conformality and homogeneity indices (HI) were recorded for comparison. The HI of the PTV (as defined by the International Commission on Radiation Units and Measurements report 83) is the ratio of $(D_{2\%}–D_{98\%})/D_{50\%}$, where $D_{2\%}$ = maximum dose received by 2% of PTV; $D_{98\%}$ = minimum dose received by 98% of PTV; and $D_{50\%}$ = the dose received by 50% of PTV. A lower HI value equates to a more homogeneous dose distribution, e.g. HI = 0 means that there is no dose gradient inside the target – perfect uniformity.

The conformation number (CN) of the PTV was also used in the statistical analysis. The CN for the PTV was calculated as $CN = (V_{T,\ ref}/V_T) \times (V_{T,\ ref}/V_{ref})$ as described by Riet et al. $V_{T,\ ref}$ is volume of the PTV receiving a dose equal to or greater than the reference dose; V_T is the volume of the PTV; and V_{ref} is the volume receiving a dose equal to or greater than the reference dose. The CN is a convenient instrument for indicating the degree of conformality with a single numerical value. A lower CN value equates to a less conformal plan and a CN of 0.60 has been used as the threshold for conformal radiotherapy [21].

Data analyses and statistics

The differences in dosimetric parameters, including mean doses to the target, $V_{T,\ ref}$, V_{ref}, PTV CN and PTV HI from the two calculations, were compared using a two-tail Student's paired t-test with a cut-off p-value < 0.05 indicating statistical significance. The correlation between the differences between CN values of the PTV from the two calculations and potential variable factors was investigated with logistic regression models. A single logistic regression model was used to investigate possible predictors for the CN differences of the PTVs between the two calculation algorithms. We used continuous variable of the predictors to do the analysis. Univariate and multivariate analyses were performed to search for dependent variable factor(s). All statistical analyses were performed in SAS software, Version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Target dosage and dosimetric parameter comparison

There were no differences identified in the mean dose to the PTV between the two calculation algorithms (Table II). However, the two-tail paired Student's t-test revealed a significant difference in the HI for the PTV between the two calculations. Compared to AAA, the Acuros XB algorithm predicted a more heterogeneous dose distribution inside the PTV. Similarly, a smaller but significant difference of CN for the PTV was also observed. The median difference in CNs of the PTVs between Acuros XB and AAA was −2.1% (range + 6.4% to −38.2%, $p < 0.0001$, two-tail paired t-test). The different dose distributions within the target caused a small but significant difference of mean doses for GTV and ITV between two calculation algorithms. The detailed calculation results are presented in Table II.

Potential predictors for variation in conformation number between the two calculations

Single logistic regression model results indicated that three factors: FEV1, number of beams and target location had strong correlations with the difference of CNs between the two dose calculations. As the median difference of CN of PTV between Acuros XB and AAA was −2.1%, a −5% was used as a cut-off for analysis. By performing the univariate

Table II. Dosimetric parameter results from two algorisms calculation (n = 77).

Parameter	Acuros XB (median)	AAA (median)	p
Mean GTV dose (%)	99.5 (97.0–102.9)	99.2 (96.6–100.9)	0.011
Mean ITV dose (%)	99.3 (96.5–102.5)	98.9 (96.1–100.8)	0.0019
Mean PTV dose (%)	97.4 (92.3–103.6)	97.4 (92.9–108.8)	0.74
V_T, ref (cm^3)	59.57 (17.60–341.58)	63.38 (18.10–355.83)	< 0.0001
Vref (cm^3)	81.84 (23.44–416.21)	85.30 (34.66–444.13)	0.0001
PTV CN	0.650 (0.394–0.790)	0.674 (0.395–0.815)	< 0.0001
PTV HI	0.088 (0.047–0.212)	0.074 (0.030–0.147)	< 0.0001

AAA, anisotropic analytical algorithm; CN, confirmation number; GTV, gross target volume; HI, homogeneity index; ITV, internal target volume; PTV, planning target volume; FEV1, volume of air exhaled in the first second.

Table III. Analyses of the continuous variable of predictor associated with CN gap more than −5% of PTV.

	Univariate analysis		Multivariate analysis	
Predictor	OR (95% CI)	p	OR (95% CI)	p
GTV	0.98 (0.94–1.03)	0.482	–	–
ITV	0.98 (0.95–1.02)	0.358	–	–
PTV	0.99 (0.98–1.01)	0.299	–	–
FEV1	0.31 (0.11–0.81)	0.0175*	0.332 (0.12–0.90)	0.0296*
Number of beam	0.55 (0.28–1.07)	0.076	0.613 (0.30–1.27)	0.1871
Body mass index	1.00 (0.92–1.08)	0.93	–	–
Tumor location	0.31 (0.06–1.51)	0.15	0.341 (0.067–17.4)	0.1958

AAA, anisotropic analytical algorithm; CI, confidence interval; CN, confirmation number; GTV, gross target volume; HI, homogeneity index; ITV, internal target volume; OR, odds ratio; PTV, planning target volume; FEV1, volume of air exhaled in the first second.

analysis, we found that FEV1, the number of beams and the tumor location were possible predictors for CN differences greater than −5 % for the PTV between the two calculations. Furthermore the multivariable analysis confirmed that FEV1 ($p = 0.0296$) was the only key predictor for the two dose calculation algorithms (Table III). The number of beams used to plan ($p = 0.1871$) and the tumor location ($p = 0.1958$) did not show significant association with the CN difference for the PTV from the two calculations.

The detailed relationship between FEV1 value and the difference in CNs of the PTVs between the two dose calculation algorithms was analyzed by a quartile of FEV1 value analysis (Figure 1). The treatment plans for two selected patients were used for comparison; Case A with a low FEV1 = 0.67 l, and Case B with a normal FEV1 = 2.58 l. Isodose lines of the reference dose in the two patients are presented in Figure 2 for the AAA and Acuros XB algorithms. The patient with the lower FEV1 (Case A) demonstrated a different distribution of the reference dose between the two algorithms which resulted

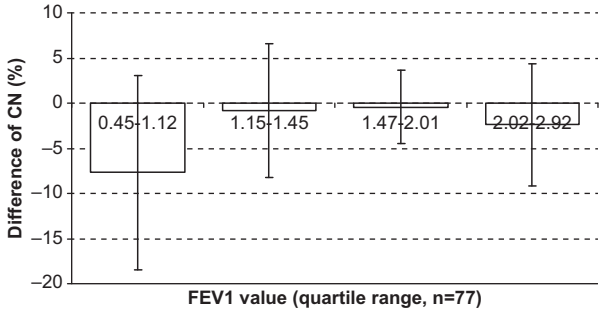

Figure 1. The relationship between the FEV1 value and the difference of CN of PTV (median and standard deviation) in two algorithms is presented by a quartile of FEV1 value.

in a significantly smaller reference volume for Acuros XB compared to AAA ($V_{ref} = 100.8$ cm^3 for Acuros XB vs. 121.0 cm^3 for AAA). The PTV dose-volume histograms (DVHs) are shown in Figure 2. It shows that the patient with a low FEV1 (Case A) had a higher heterogeneity and smaller volume of PTV receiving the reference dose ($V_{T, ref} = 89.0$ vs. 102.2 cm^3) in the Acuros XB algorithms dose calculation compared to AAA. Compared to the Case A, there was no such phenomenon in Case B who had a normal FEV1 value ($V_{ref} = 107.7$ cm^3 for Acuros XB vs. 101.8 cm^3 for AAA and $V_{T, ref} = 75.7$ vs. 74.4. cm^3).

Discussion

The availability of a novel deterministic patient dose calculation algorithm in the clinic brings forth new challenges in our ability to understand the impact of this change. The Acuros XB algorithm provides accurate dose calculation in a heterogeneous medium, by accounting for the individual voxel chemical composition. Improved voxel density to biological material assignment is one of the new features in Eclipse version 11. Current AAA and other algorithms of its genre have inherent limitations within heterogeneous media, as they convert a heterogeneous medium to its standard reference medium-water by using electron density scaling whereas the Acuros XB algorithm computes the absorbed to the medium contained in the dose calculation voxel itself [6]. Acuros XB implementation includes a photon beam source model which is shared with AAA. However, the radiation transport calculation in Acuros XB results in the dose to the medium determined from the calculated electron fluence [7]. Aarup et al. previously reported that AAA seems to be a good alternative to MC for lung densities > 0.2 g/cm^3. However, in cases where the lung density becomes close to 0.1 g/cm^3, the difference compared to MC may be of clinical significance [19]. The accuracy of AAA in SBRT is questionable, given the small tumor size and the surrounding lung tissue and/or proximity to the chest wall/rib. Several other investigators have clearly addressed these concerns [6,7]. In a dosimetric study, Kan et al. have reported the benefit of using Acuros XB in nasopharyngeal carcinomas [22].

In this clinical study, for a cohort of 77 lung SBRT patients, we found no significant differences in the mean dose to the target, as determined from the two dose calculations with the same MU per beam. These findings are similar to what has been reported in the literature [9,12,22,23]. However, there was a statistically significant difference observed for the CN of the target, between the two algorithms (Table II). The reason for this difference is attributed to the modeling of the heterogeneity of lung tissue in the Acuros

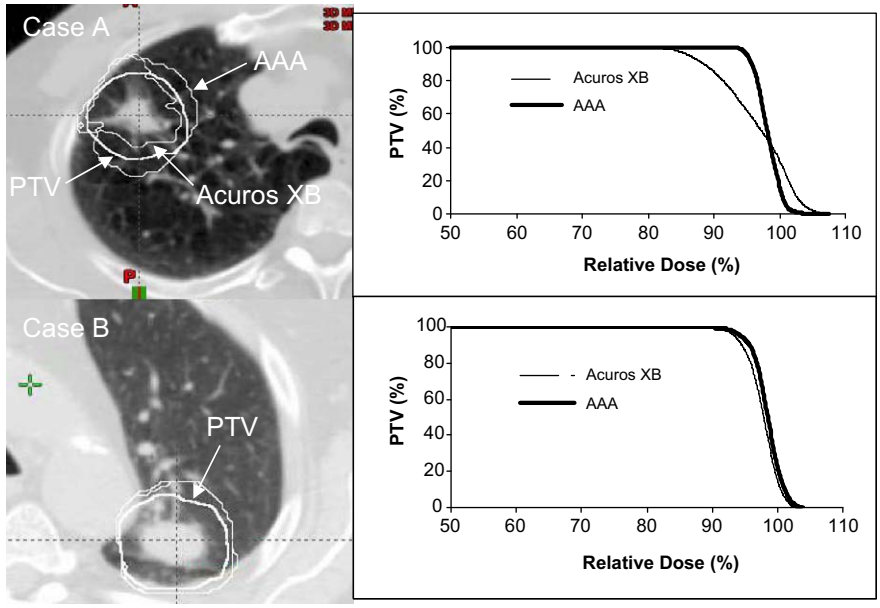

Figure 2. Isodose plot of a reference dose to the target in patients with low FEV1 (Case A) and normal FEV1 (Case B) by Acuros XB and AAA calculation and their correlated PTV dose-volume histograms.

XB algorithm, in comparison to AAA as reported by others [9,10,16,24]. This finding supports previous observations that AAA overestimates the dose near the edge of the heterogeneity [24], and more obviously in the emphysematous lung due to its lower HU values (Figures 1 and 2). The clinical impact of this slight over estimation in target isodose might not impact the local control significantly. However, the slight change in the dose distribution of the target between the two dose calculations can cause a significant difference to the HI of target (Table II and Figures 1 and 2). Whether or not this slight dose distribution difference could influence tumor control or normal tissue complication probabilities, is worth investigating.

Therefore the primary objective of this study was to identify patient-related factors causing the change in dose distribution, specifically the different CNs of the target between the two algorithms. The single regression analysis between the predictive factors and CN difference resulted in FEV1, number of beams and target location as possible variables of interest. Setting a threshold of larger than 5% in CN and using univariate and multivariate analysis, we confirmed that the value of FEV1 was the only key factor in causing a variation in CN of the PTV, for the two algorithms (Table III).

A lower FEV1 represents poor pulmonary function, which means the lung parenchyma contains more air sacs than the normal lung tissue. The value of FEV1 is one of the criteria used to diagnose the severity of chronic obstructive pulmonary disease (COPD)/emphysema. The CT image of such a COPD lung would result in lower Hounsfield Units (HUs) compared to a normal lung [18]. The current study supports that dose calculation by Acuros XB algorithm is able to account for the lower lung density. It is well known that a large number of early stage lung cancer patients who are unfit for surgery and are treated with SBRT have poor lung function. In the current study, the original treatment plans were optimized for AAA, not the Acuros XB algorithm. With adoption of the Acuros XB in future studies, an optimized dose plan will be more accurate and superior in terms of dose coverage in lung SBRT [9,10]. An attempt to find a cut-off FEV1 from the current cohort in order to demonstrate a significant benefit of using Acuros XB was not successful due to large deviations in the data. Instead of that we chose to perform a FEV1 value quartile analysis as shown in Figure 1.

In terms of the anatomic location of the target, a recent study showed that tumors located in the central lung are surrounded by relatively denser (higher HU) lung tissue than those located in the peripheral lung [17]. In the current study, using a single regression model we found an elevated estimated regression coefficient relating tumor location and CN difference in the two algorithms (Test statistic value 1.46, $p = 0.15$). However, both the uni- and multivariable model analyses, revealed no strong association with the variation of CN for PTV. This negative finding might be due to a small number of cases in our cohort (14 central vs. 63 peripheral) and setting up of -5% threshold level. The number of beams used in external beam planning is important in order to gain target dose conformity. However, this parameter was not responsible for the differences between

the two algorithms. Neither was the patient BMI, nor the target volume, i.e. GTV, ITV and PTV.

There are several studies using Acuros XB comparing dosimetric parameters for various treatment sites and techniques [7,9,12,16,22]. Few of them addressed the clinical impacts of Acuros XB versus the current generation of dose calculation algorithms especially for lung tissue. We have shown that the observed significant differences in conformation number for the target are related to poor lung function. In this clinical study using a cohort of 77 lung SBRT cases, we have shown that the patient's pulmonary function influences the difference in target dose distributions between the Acuros XB algorithm and AAA. This is due to more accurate modeling of the heterogeneity of lung tissue by the Acuros XB algorithm, in comparison to AAA. The accuracy of Acuros XB algorithm could be used to advantage in patients with compromised pulmonary function in lung SBRT.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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