ACTA ONCOLOGICA
2021, VOL. 60, NO. 10, 1296–1300
https://doi.org/10.1080/0284186X.2021.1950926

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ORIGINAL ARTICLE

Planning target volume density impact on treatment planning for lung stereotactic body radiation therapy

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ABSTRACT

Background: To evaluate the impact of the planning target volume (PTV) density on treatment planning for lung Stereotactic Body Radiation Therapy (SBRT).

Material and methods: The PTV coverage was analyzed in two groups of 40 lung SBRT patients. One group had PTV density $<0.5\,g/cm^3$, while the other group had PTV density $>0.5\,g/cm^3$. The treatments were planned in Pinnacle 9.10, using the collapsed cone convolution (CCC) algorithm. The prescribed dose was 60 Gy to the PTV in 4–8 fractions. Respecting constraint for the PTV coverage (D98% > 95%), we compared changes in the isodose line prescription, the number of monitor units (MU), maximum dose (D_{max}), irradiated volume covered with 30 Gy (V_{30Gy}), and the optimization planning volume (OPV).

Results: For the same median values of the PTV coverage (98.3%), the differences are presented with median values between lower and higher density than $0.5\,g/cm^3$. The isodose line prescription was 83 *vs.* 90% ($p < 0.0001$), the MUs were 2294 *vs.* 1655 MU ($p < 0.0001$), D_{max} was 74.26 *vs.* 68.09 Gy ($p < 0.0001$), V_{30Gy} was 117.03 *vs.* 104.81 cc ($p = 0.04$), and OPV was 28.48 *vs.* 39.35 cc ($p < 0.001$). By overriding the ITV density to $0.8\,g/cm^3$, the isodose line prescription decreases. The D_{max} and MUs decrease by 7%, V_{30Gy} by 34%, and OPV by 70%.

Conclusion: To obtain similar PTV coverage for PTV which is $<0.5\,g/cm^3$, a larger margin irradiating a large OPV was used. More MUs and a higher maximum dose were delivered. For the PTV density of $\leq 0.36\,g/cm^{3,}$ overriding is recommended to reduce the dose and irradiated volume.

ARTICLE HISTORY
Received 30 March 2021
Accepted 26 June 2021

KEYWORDS
Lung cancer; density; planning target volume; stereotactic body radiation therapy

Background

The complexity of lung stereotactic body radiation therapy (SBRT) treatment planning depends on lung tissue density (heterogeneous organ), in comparison to other organs or the tumor's density. In radiation therapy, a computed tomography (CT) scan is used to determine tumor and organ density, shape, and localization [1]. The differences between the organs and the tumor are distinguished by the shade of gray, with Hounsfield units (HU) or electron density and mass density (g/cm^3) [2].

Using a helical CT scan, the gross tumor volume (GTV) could be contoured from a single series of static images, taken at some arbitrary phase of the respiratory cycle (screenshot of the patient anatomy). In this case, the GTV density will depend on the GTV localization [3]. Lung tumors are generally mobile. The evaluation of tumor motion can be performed using four-dimensional computed tomography (4 D-CT) within the respiratory cycle. This motion defines the internal target volume (ITV) [4]. The mean ITV density decreases when GTV motion increases. To account for patient motion and geometric uncertainties, the planning target volume (PTV) was generated. Increasing margins during treatment planning decrease the mean density in the treatment volume [5]. Lower density inside the PTV reduces the number of Compton interactions with irradiated tissue, decreasing the dose to the GTV [6]. Low electron density in the lung can impact treatment planning. Build-up equilibrium must be ensured in the interaction of greater photon fluence and lung tissues with relatively low electron density [7,8]. The heterogeneity between tumor density and lung density can be resolved with sophisticated treatment planning algorithms. Several studies evaluated the impact of the electron density to the treatment planning using different phantoms that underwent different treatment planning conditions, such as static or dynamic beams, conventional or stereotactic doses, homogenous lung, and target densities, larger ITV to PTV margin, and with different algorithms, such as analytic anisotropic algorithm (AAA), Acuros XB (AXB), pencil beam, collapsed cone convolution (CCC), and Monte Carlo (MC) simulation [6–20].

Comparing to the previously cited studies, in this study, the impact of the PTV density on treatment planning was evaluated using dynamic arcs and the CCC algorithm, for lung stereotactic body radiation therapy (SBRT) treatments with small ITV to PTV margin, depending on the inhomogeneous densities in real lung cancer patients. The complexity of treatment planning was evaluated for PTV density lower and

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higher than 0.5 g/cm^3. Also, the impact of the overriding density for lower PTV density and its impact on treatment planning parameters and dose delivered to the organ at risk (OAR) was evaluated.

Material and methods

Patient selection

Eighty patients, 48 males, and 32 females were retrospectively analyzed, depending on the PTV density. The PTV density, representing the densities for all treatment volumes, was evaluated by referencing a helical CT scan (without stereotactic body frame), using the Pinnacle 9.10 treatment planning system (TPS). Two patients' groups, 24 males and 16 females per group, were naturally emerged with PTV density which was lower and higher than 0.5 g/cm^3. Forty patients, 16 in the upper lobe and 24 in the lower lobe, had PTV density lower than 0.5 g/cm^3, while forty patients, 26 in the upper lobe and 14 in the lower lobe, had PTV density higher than 0.5 g/cm^3.

Data acquisition

CT acquisition was performed using a GE LightSpeed scan with 16 slices (General Electric Medical Systems, Waukesha, WI, USA), equipped with the Real-Time Positioning Management system (RPM, Varian Medical Systems, Palo Alto, CA, USA). Following institutional protocol, lung SBRT patients were scanned with two helical CT scans, with and without a stereotactic body frame. This was followed by a 4 D-CT scan, using the following parameters: 0.7 s/rotation period, 120 kV, mA ranging from 10 to 440 mA, 16 slices detector and a slice thickness of 1.25 mm, with a beam collimation width of 20 mm, and field of view (FOV) of 55 cm. The tube current modulation (TCM) was turned on. The 4 D-CT scan was acquired in retrospective mode. The 4 D images were reconstructed retrospectively, in ten phases that ranged from 0 to 90%, with increments of 10%.

Delineation

The delineation was performed using the Advantage Sim software (General Electric Medical Systems, Waukesha, WI, USA). The GTV was created from the helical CT scan without a stereotactic body frame. The ITV was created from all ten phases of the respiratory cycle, to take into consideration the overall tumor motion. The PTV was generated from the ITV by adding a uniform margin of 3 mm.

Treatment planning

Treatment was planned using the Pinnacle 9.10 TPS and calculated with 6 MV photon beams with a dose rate of 600 MU/min, for 2–4 partial dynamic conformal arcs (DCA), using the CCC algorithm with a grid size of 2 mm [12]. The prescribed dose was 60 Gy to the PTV in 4–8 fractions, normalized at isodose lines that were >80%. To ensure PTV coverage at all slices and planes, the optimization planning volume (OPV) was created for all PTV densities. Various margins were used to create OPV, predominantly in the superior-inferior (SI) direction. Respecting constraint for the PTV coverage (D98% > 95%), we compared changes in the isodose line prescription, the number of monitor units (MU), maximum dose (D_{max}), the irradiated volume covered with 30 Gy (V_{30Gy}), and OPV.

Using the Pinnacle 9.10 TPS, the density was evaluated for the lung, GTV, ITV, and PTV for eighty patients.

For patients with PTV density lower than 0.5 g/cm^3, the ITV volume was overridden. Overriding was performed on the ITV because the ITV volume covers the entire trajectory of tumor motion, which decreases its density within the PTV. The plans were recalculated and compared with plans that were performed without an override.

Data analysis

The results were presented with median and range values because large outliers lead to a large skew in mean values. The comparison of median values was performed using a Wilcoxon-signed rank test, with a statistical significance level of $p < 0.05$, using Origin Pro 8.6 software (Northampton, MA, USA).

Results

The lung, GTV, ITV, PTV, and OPV densities are presented with median values and their range, while the statistical significance of the results is presented with the p-value (Table 1).

The variation in the density within the PTV was presented depending on lung density, initial GTV density, and ITV density due to tumor motion, for the PTV's density lower than 0.5 g/cm^3 in Figure 1(a) (screenshot of the patient anatomy for a particular patient) and higher than 0.5 g/cm^3 in Figure 1(b) (screenshot of the patient anatomy for a particular patient).

For ten patients, the PTV's density was increased about 0.20 g/cm^3 (from 0.72 to 0.93 g/cm^3, an example of densities taken from the particular patient) when GTV overlapped with structures (such as the heart, esophagus, bronchial stump, trachea, mediastinum, or chest wall) during motion and/or when localized near tissue with high density (about 1 g/cm^3). In seven cases, the GTV was localized in the center of the parenchyma, having a greater amplitude of motion, which decreased the PTV density by about 0.50 g/cm^3 (from 0.90 to

Table 1. Median values of the density measured from the volume of interest using the Pinnacle 9.10 treatment planning system.

Contour	Density < 0.5 g/cm^3	Density > 0.5 g/cm^3	p-Value
Lung (g/cm^3)	0.21 (0.14–0.31)	0.26 (0.15–0.38)	<0.001
GTV (g/cm^3)	0.73 (0.37–0.90)	0.88 (0.69–1.03)	<0.0001
ITV (g/cm^3)	0.49 (0.31–0.80)	0.77 (0.56–1.05)	<0.0001
PTV (g/cm^3)	0.35 (0.20–0.48)	0.61 (0.50–0.99)	<0.0001
OPV (g/cm^3)	0.28 (0.15–0.44)	0.53 (0.33–0.96)	<0.001

GTV: gross tumor volume; ITV: internal target volume; PTV: planning target volume; OPV: optimization planning volume.

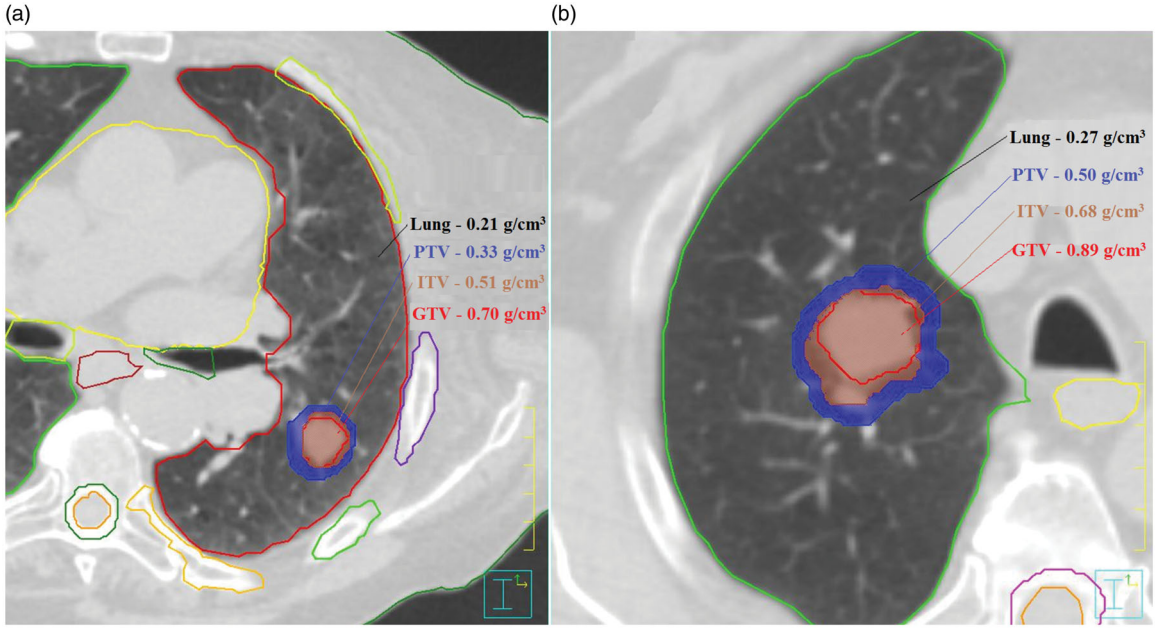

Figure 1. Values of the lung, GTV, ITV, and PTV densities, presented for a particular patient depending on the PTV density lower than 0.5 g/cm^3 (a) and higher than 0.5 g/cm^3 (b).

Table 2. Median (range) value of the PTV coverage, isodose line prescription, number of monitor units, maximum dose, irradiated volume covered with 30 Gy, and optimization planning volume, evaluated between the PTV density lower and higher than 0.5 g/cm^3.

Parameters	Density $<$ 0.5 g/cm^3	Density $>$ 0.5 g/cm^3	*p*-Value
PTV coverage (%)	98.3 (95–99.8)	98.3 (95.4–99.8)	=0.390
Isodose prescription (%)	83 (76–91)	90 (81–96)	<0.0001
Monitor unit (MU)	2294 (1087–3120)	1655 (936–2416)	<0.0001
Dose max (Gy)	74.26 (66.07–79.90)	68.09 (64.79–77.96)	<0.0001
V_{30Gy} (cc)	117.03 (9.98–398.34)	104.81 (23.79–681.18)	=0.04
OPV (cc)	28.48 (6.04–79.8)	39.35 (9.07–188.2)	<0.001

PTV: planning target volume; Dose max: maximum dose; V_{30Gy}: irradiate volume covered with 30 Gy; OPV: optimization planning volume.
Statistical significance of the results was presented with *p*-value.

0.36 g/cm^3, an example of densities taken from the particular patient).

For similar PTV coverage, the differences between the isodose line prescription, MUs, D_{max}, V_{30Gy}, and OPV were evaluated from lower to higher PTV density than 0.5 g/cm^3 and, as such, presented in Table 2.

The patient receiving the higher number of MUs (3120 MU) had the tumor located in the parenchyma with a 20 mm amplitude of tumor motion, which increased the OPV to 79.8 cc and V_{30Gy} to 398.34 cc.

For patients with PTV density lower than 0.5 g/cm^3, the ITV's density was overridden (0.8 g/cm^3), and changes in the parameters of treatment planning were compared with the treatment plan without override (Table 2) and presented in Table 3.

By overriding the ITV's density, an important difference in results was obtained for the PTV density between 0.20 and 0.36 g/cm^3, then subsequently between 0.36 and 0.48 g/cm^3 (Table 3). Recalculated plans show a decrease in results: the isodose line prescription to 5%, number of monitor units to 151 MU, the maximum dose to 3.7 Gy, V_{30Gy} to 25.2 cc, and OPV to 18.1 cc.

The difference between the dose delivered to the OARs, with and without overriding the density of the ITV, was presented in Table 4.

Table 3. Median (range) differences between results obtained before and after overriding the ITV density for isodose line prescription, number of monitor units, maximum dose, irradiated volume covered with 30 Gy, and optimization planning volume.

Parameters	0.20–0.35 g/cm^3	0.36–0.48 g/cm^3	*p*-Value
Isodose prescription (%)	4 (2–6)	0.5 (0–1)	<0.0001
Monitor unit (MU)	88 (40–162)	5 (3–11)	<0.0001
Dose max (Gy)	3.7 (1.1–5.3)	1.1 (0.8–1.6)	<0.0001
V_{30Gy} (cc)	22.3 (2.8–41.2)	8 (3–16)	<0.0001
OPV (cc)	14.3 (4.2–21.3)	2 (0–3.2)	<0.0001

Dose max: maximum dose; V_{30Gy}: irradiate volume covered with 30 Gy; OPV: optimization planning volume.
Statistical signification of the results was presented with *p*-value.

Table 4. Difference between doses delivered to the OARs, with and without overriding the ITV density.

Organ	Without override	With override	Difference
Spinal cord (Gy)	10.91 ± 2.32	10.38 ± 2.16	0.53 ± 0.55
Heart (Gy)	9.19 ± 3.12	8.91 ± 3.01	0.28 ± 0.12
Esophagus (Gy)	13.18 ± 2.76	12.58 ± 2.49	0.60 ± 0.22
Bronchial stump (Gy)	13.56 ± 4.17	12.98 ± 3.89	0.58 ± 0.30
Lungs (%)	5.22 ± 2.60	3.40 ± 2.48	1.82 ± 0.46
Ribs D_{max} (Gy)	52.63 ± 4.34	48.80 ± 4.09	3.83 ± 0.64

D_{max}: maximum dose.

Discussion

In this study, the treatment planning of lung SBRT was evaluated depending on the PTV density for eighty patients.

Evaluating the PTV density, we found that density changes depending on the GTV localization, tumor motion, and density of the surrounding tissue, where inhomogeneity within the human body varies depending on patient morphology and tumor localization. For 25% of the patients with GTV localized near tissue with high density, such as the heart, esophagus, bronchial stump, trachea, mediastinum, or chest wall, or with it overlapping with these structures during motion, the PTV density increases by 23%. With 18% of the patients, with a GTV with greater amplitude of tumor motion localized in the parenchyma, being surrounded with lung tissue with lower density, the PTV's density decreases up to 60%. Due to the loss of electron equilibrium in low and inhomogeneous lung density, the impact on treatment planning requires an increase of photon fluence to ensure the GTV coverage. Large tumor motion, increase the ITV volume, decreasing its density. To take into consideration any geometrical uncertainty, the PTV was created from ITV volume, adding a uniform margin of 3 mm according to Institutional protocol, decreasing the density even more. However, the impact of the PTV density will be less for the tumors located near the OAR, great blood vessels, or chest wall.

The changes in the treatment planning parameters were analyzed for PTV density which is lower and higher than 0.5 g/cm^3, separately and in two groups, per forty patients. Treatment planning was performed without overriding the density for all eighty patients. To obtain similar PTV coverage (D98% $>$ 95%), the PTV with lower density increases: the isodose line prescription by 8%, number of MUs by 28%, maximum dose for 6 Gy, $V_{30\,Gy}$ by 15%, and OPV by 30%. Miura *et al.* found that when lung density is decreased, the dose to the PTV reduces by more than 20% between the planned and delivered dose, using MC calculation for the PTV margin of 8 mm [13]. This margin is still large compared to the margin of 3 mm in this current study. Higgins *et al.* used a similar margin of 3.5 mm to ensure the PTV coverage, for variable lung and target densities [19].

For all forty patients with a density lower than 0.5 g/cm^3, by analyzing treatment planning after overriding density, the limit to the planning was found near the density of 0.36 g/cm^3. For twenty patients with PTV density between 0.37 and 0.48 g/cm^3, recalculated treatment plans were statistically insignificant ($p > 0.05$), after overriding the ITV density to 0.8 g/cm^3. On the other hand, overriding the ITV density for the PTV density between 0.20 and 0.36 g/cm^3, recalculated plans show statistically significant differences (Table 3). The results increased 7% for the isodose line prescription, 7% for the number of monitor units, 7% for the maximum dose, 34% for the $V_{30Gy,}$ and 70% for the OPV. Small changes were found in dose delivered to the OARs, overriding the ITV density, decreasing dose to a maximum of 1 Gy for the spinal cord, heart, esophagus, and bronchial stump, lung to a maximum of 2%, and ribs to a maximum of 4 Gy. Even the isodose line distribution changes due to a heterogeneous medium (Table 2).

Similar results were found in Fu *et al.* study, with recalculated treatment plans for twelve patients, in the Pinnacle TPS, overriding the PTV density. They reported that isodose prescription changes with the CTV localization. MU reduction (10%) was found for small CTV ($<$1.2 cc) and 3% for the remaining patients [14]. These results well in tune with the results in the current study.

Wiant *et al.* found that overriding might lead to reductions in lung dose, a decreased need for MLC shaping or modulation, and an increased efficiency in treatment planning and delivery [6]. Healy *et al.* found that the geometric and dosimetric dose coverage and conformity improved overriding the PTV density for smaller tumors ($<$22-mm diameter) [17]. Even if Wiant *et al.* and Healy *et al.* studies were performed on phantoms with different algorithms and treatment planning conditions, their results confirm our hypothesis that the dose calculation accuracy in a lower density medium (lung) is more sensitive to density variation due to the loss of electron equilibrium, increasing complexity of the treatment planning, especially in lung SBRT treatment.

The MC simulation can handle tissue heterogeneity and provides a more accurate dose to a lung tumor, but its clinical use is not available in all TPS [15,19]. The effect of density variation on photon dose calculation was evaluated by Liu *et al.*, which reported that dose error in target volume can be limited between 2 and 3% if the density variation is restricted, with a CT number for lung material of ±20 HU, using MC [18]. These results are in contrast with Mohatt *et al.* study, which predicted that dose error at isocenter is $<$2% using AAA and AXB algorithms, over a target density variation spanning a delta on the order of 200 HU [8].

Zvolanek *et al.*, using multiple TPS, found the dose-differences to be small for Type C computations [19]. Aarup *et al.* found that an adequate alternative to MC for the target dose can be ensured using the AAA and the CCC algorithm [20].

The treatment plan verification of isodose lines is still a serious problem. At the moment, an adequate phantom that recreates real conditions that can distinguish the corresponding density of the lung and the treatment volume (GTV, ITV, and PTV) does not exist. Another issue is that the impact of the overriding density (decrease in dose and treatment volume) between treatment planning and treatment delivered cannot be evaluated for patients with lower PTV density (0.36 g/cm^3).

Conclusions

In this study, the PTV density impact on treatment planning was investigated using the Pinnacle 9.10 TPS and the CCC algorithm. From the results of this study, one can conclude that the PTV density depends on the initial GTV density, localization, and motion, as well as the density of the surrounding tissue.

For the PTV with low densities ($<$0.50 g/cm^3), to obtain similar PTV coverage as PTV with higher density, a larger margin and number of MUs were used, increasing the maximum dose and irradiated volume.

For the PTV density $\leq$0.36 g/cm^3, it is recommended to override the ITV to 0.8 g/cm^3, improving and simplifying treatment planning, without any impact on treatment safety.

However, the real problem remains between isodose lines presented in the TPS and within the real lung. It is recommended to develop the phantom with realistic densities to take into consideration isodose line distribution. The proposed idea will be subject to future research.

Disclosure statement

The authors report no conflicts of interest.

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