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CBCT-based dosimetric verification and alternate planning techniques to reduce the normal tissue dose in SBRT of lung patients

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Original Article

Abstract

Purpose: Confirmation of treatment delivery accuracy in stereotactic body radiotherapy (SBRT) of lung tumors suggests the possibility of treatment margin, or aperture reduction. In this investigation, the dose delivery to lung tumors using SBRT techniques was verified, and the feasibility of normal tissue sparing via aperture reduction or altered prescription isodose line was assessed. **Methods:** Planned and delivered doses to the gross tumor volume (GTV) and planning target volume (PTV) were compared for 10 patients using planning CT and conebeam CT image. Potential for reduction in normal tissue dose were assessed using 2 alternate treatment plans – reduced PTVs and alternate prescription techniques. Plans were assessed using conformity index, homogeneity index and the ratio of 50% / 100% isodose volumes ($R_{50\%}$). **Results:** The planned and delivered mean doses were consistent to within 4%. However, the mean dose delivered to the GTV exceeded the prescription dose (Rx) by 19% and is consistent with our planning technique of prescribing to the 80% isodose line. When reducing treatment margins and retaining a constant dose-volume constraint, block margins had to be increased which produced a constant effective field aperture outside of the GTV. Prescription to a lower isodose line using stereotactic-like planning techniques yielded the only method by which the volume of the prescription isodose could be affected, although this yielded increases in normal tissue dose due to the increased monitor units required. Conversely, conventional prescription techniques using wider field apertures were effective in reducing absolute values of normal tissue dose. Although dose conformity was similar across different prescription isodose lines, homogeneity index and $R_{50\%}$ values were significantly different in the 60%-70% prescription isodose line plans than the 80%, 90% prescription plans. **Conclusion:** Traditional margin reduction techniques did not affect a reduction in the volume of normal tissue irradiated to the prescribed dose. Prescribing to low isodose lines yields reduced volumes of the prescribed dose, but at the expense of normal tissue dose.

Keywords: SBRT; Dose Verification; Dose Optimization; Margin Reduction; Prescription Isodose

Introduction

Stereotactic body radiation therapy (SBRT) is a widely used treatment modality for early-stage non-small cell lung cancer (NSCLC).[1] Stereotactic plans need not only optimum dose conformity within the target, but also sharp dose fall off in the normal tissue. There is a mature literature on the efficacy of SBRT, and studies vary in terms of the specifics used for treatment planning, immobilization and daily setup.[2, 3] We began the present investigation to study the degree to which our planning and treatment techniques result in dosimetric accuracy.

The results supported the assumption of dose delivery accuracy and prompted an investigation into the feasibility of reducing the planning target volumes (PTVs) for this class of tumors. This latter investigation revealed certain potentially counter-intuitive aspects to the prospects of margin reduction for these very small tumors. Herein, we present our findings.

Typical SBRT planning strategies presume there to be unpredictable motion of the gross tumor volume (GTV) within the PTV, thus justifying the practice of treating volumes of uninvolved normal tissue. The amplitude of lung tumor motion is largest along the superior-inferior direction and can have significant dosimetric impact.[4] Several management strategies have been developed including abdominal compression to reduce the amplitude of target motion [5, 6] respiratory gated treatment [7], and patient coaching[8]. Many clinics combine more than one of these strategies and hence it is conceivable that the GTV motion is less than anticipated.[2] As

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such, current PTV margin recommendations may require additional scrutiny. In this study, we identified 2 alternate treatment planning methods that could potentially reduce the normal tissue dose and these were reduced PTV margins and alternate prescription techniques.

Further, we note that there are potential differences between the dose presented on the treatment plan, the prescribed dose (Rx) and the presumed delivered dose accounting for excursions of the GTV within the PTV volume. Yeung *et al.*[9] and Grills *et al.*[10] measured daily setup using cone-beam CT (CBCT) and suggested the possibility of margin reduction in lung cancer patients. Galerani *et al.*[11] had performed manual segmentation of tumor and normal structures directly on the CBCT image followed by calculation of dose distribution.

However, the Hounsfield unit (HU) inaccuracies that are present in the CBCT image limit the accuracy with which the dose can be calculated. Rather than a direct dose calculation on CBCT data sets, Yang *et al.*[12] used the HUs from planning CT (pCT) images after registering to the CBCT images in order to improve the accuracy of dose calculation, an approach used in this study.

Methods and Materials

Simulation and treatment

Ten patients treated for primary lung cancer with SBRT on a conventional 21EX linear accelerator (LINAC) (Varian Medical Systems, Palo Alto, CA, USA) were studied, as shown in **Table 1**. LINAC was commissioned with 40 pairs of 5 mm thick multileaf collimators and 6 MeV photon beam for SBRT. Patients were immobilized during simulation and treatments using a stereotactic body frame (Elekta, Stockholm, Sweden), vacuum shaping bag (Vac-lock, MED-TEC Inc., Orange City, IA) and abdominal compression.

Patients underwent free-breathing 3D-CT scans using a GE LightSpeed 16-slice CT scanner (GE Healthcare, Waukesha, WI) without any formal coaching or intravenous contrast. 4D-CT was not performed on these patients that are a part of this retrospective study. Before each fraction, a CBCT scan was acquired using an onboard imaging system (Varian Medical Systems, Palo Alto, CA, USA).

A total of ten free-breathing pCT scans and thirty eight CBCT scans were acquired. Three-dimensional conformal planning was performed using both coplanar and non-coplanar beams with XiO treatment planning system (ver 4.50, CMS, St. Louis, USA). A convolution/superposition algorithm with heterogeneity corrections applied on a grid size of $2 \times 2 \times 2$ mm^3 was used for calculations.

TABLE 1: Tumor characteristics and fractionation schemes of the 10 patients in our study.

Characteristic	Value or Mean	Range
No of patients studied:	10	
Male	3	
Female	7	
Age at diagnosis (yrs)	68.4	57 – 78
GTV volume in pCT (cc)	11.3	1.6 – 24.3
PTV volume in pCT (cc)	42.9	12.1 – 81.6
Fractionation:		
4×12 Gy	6	
3×18 Gy	2	
3×20 Gy	1	
5×11 Gy	1	
Tumor distribution:		
Right upper lobe	5	
Right middle lobe	2	
Right lower lobe	0	
Left upper lobe	2	
Left lower lobe	1	
# Non-coplanar fields used:		
8	2	
10	8	

Image registration and transfer of contours

The pCT image with segmented contours and the pre-treatment CBCT images were transferred to the Focal-Sim workstation (CMS, St. Louis, USA). Rigid registration was performed between the pCT and CBCT images using the target anatomy and verified by the physician. The contours of regions of interest (ROI) that were transferred following registration and corrected by the physician include GTV, PTV and organs at risk (OAR) including spinal cord, esophagus, lungs and heart.

The uncertainty in GTV contouring was assessed by scanning a test object that was oscillated with the QUASAR™ respiratory motion phantom (Modus Medical Devices, Ontario, CA). pCT and CBCT scans of the phantom were acquired using our clinical techniques and the known test object volume was then compared to that of the contoured volume. The error bars associated with the reported tumor volume changes were derived from this motion phantom study.

Comparison between prescription dose, planned dose and the delivered dose

Contours of the ROIs were drawn on the pre-treatment CBCT image. These were transferred from the pre-treatment CBCT image onto the pCT image after registration and corrected by the physician. Due to restricted field of view (FOV) of the CBCT image compared to the pCT image, the planned dose was calculated using pCT image within the FOV of CBCT image. In order to improve the accuracy of the planned and delivered doses calculations from the dose volume histogram (DVH), the HU values of only the pCT image was used in dose calculation. Calculations of dose delivered

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on a fraction were based on the treatment day ROIs transferred from the corresponding pre-treatment CBCT onto the pCT.

Reduction in the PTV treatment margin

In this study, we define PTV treatment margin as the margin that is added to the GTV and in all clinical plans these were 5, 5 and 10 mm along the lateral, anterior/posterior and superior-inferior axes, respectively. We assessed the potential for reducing the PTV treatment margin by creating five test plans from the original treatment plan for each patient. Test plans were denoted as "PTV_X_Y_Z", referring to the PTV treatment margins of X, Y, and Z mm along the lateral, anterior/posterior and superior-inferior axes, respectively. The test plans created in our study were PTV_5_5_10, PTV_5_5_5, PTV_3_3_7, PTV_3_3_3 and PTV_1_1_1.

In designing the test plans, we applied the dose-volume constraint that at least 95% of the PTV received 95% of Rx: PTV_X_Y_Z V95%Rx > 95% for each of the 5 test plans. In this study, we define the block margin as the margin that is added to the PTV in order to obtain the desired dose constraint. Majority of SBRT fields need a block margin of 2 mm and can go up to 5 mm. The field aperture, defined by the multi-leaf collimator (MLC) position, was opened outside the PTV_X_Y_Z by a block margin to account for the beam penumbra. In other words, field aperture is the sum total of the PTV and the block margin. In order to meet the dose-volume constraint of PTV_X_Y_Z, the corresponding block margin was incremented along all 3 axes in steps of 1 mm starting with 0 mm. For each of the five test plans prescribed at the 80% isodose line, the lowest block margin needed for meeting the dose-volume constraint was applied. The process is outlined in **Figure 1** in which the GTV is displayed in red, PTV treatment margin in light grey, block margin is transparent and the field aperture is defined by the inner edge of the MLCs in green. **Figure 1(a)** corresponds to PTV_5_5_10 meeting the dose-volume constraint with 0 mm block margin. While the PTV_3_3_3 fails to meet the dose-volume criteria with 0 mm block margin in **Figure 1(b)**, the same is met with 5 mm block margin as shown in **Figure 1(c)**. The corresponding absolute volume covered by the 100%, 95%, 50% and 20% of prescription isodose lines were recorded for each of the test plans.

Changes to prescription isodose line

We studied the dosimetric impact of changes in the prescription isodose line, with the intent of reducing the irradiated volume of normal tissue.[13] We tested prescriptions to 60%, 70%, 80% and 90% isodose lines, in each of the test plans upon meeting the dose-volume constraint PTV_X_Y_Z V95%Rx > 95%. This choice of prescription techniques is supported by RTOG protocols (RTOG 0915, RTOG 0618) and represents a range of treatment philosophies. For the purposes of this study, we construct the following definitions of the prescription methodologies:

- Full SRS: 60% of global maximum
- Moderated SRS: 70% of global maximum
- Aggressive conventional: 80% of global maximum
- Full conventional: 90% of global maximum

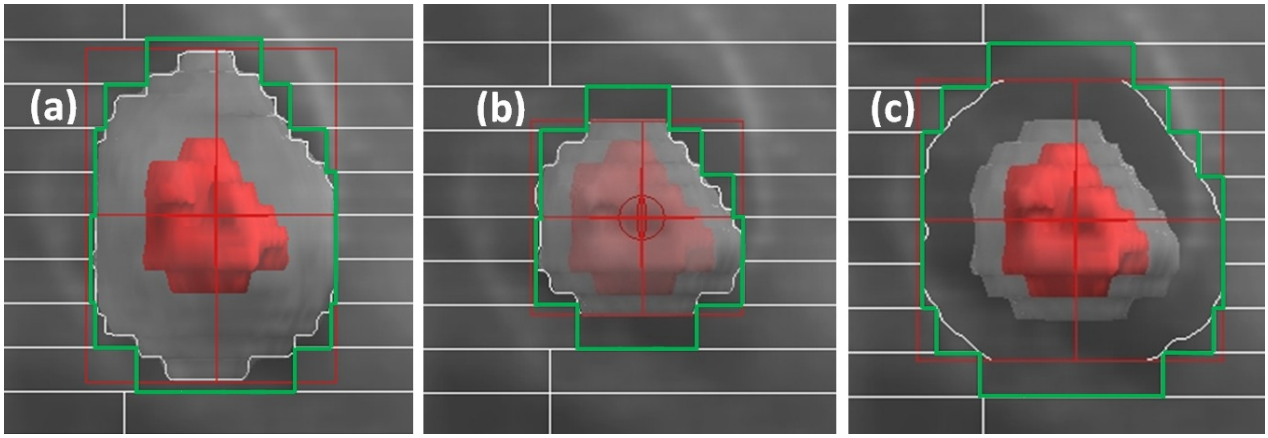

FIG. 1: Plot showing the importance of choosing an optimum block margin in order to meet the dose-volume constraint of the PTV. The GTV is displayed in solid red, PTV treatment margin in white, block margin is transparent and the field aperture is defined by the inner edge of MLCs in green. (a) Dose-volume constraint for PTV_5_5_10 (V95%Rx = 99%) is met using 0 mm block margin; (b) While the dose-volume constraint for PTV_3_3_3 (V95%Rx = 80.1%) fails with 0 mm block margin; (c) It passes (V95%Rx = 95.9%) with 5 mm block margin.

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Plan evaluation

The impact of varying the prescription methodology was assessed by measuring the absolute tissue volume contained within the 100%, 95%, 50% and 20% of the prescription dose as well as global maximum dose. Conformity index (CI) was defined based on International Commission on Radiation Units and Measurements (ICRU) Report 62 as:

$$CI = \frac{Prescription\ Isodose\ Volume}{Planning\ Target\ Volume}$$

Homogeneity index (HI) was defined as:

$$HI = \frac{D_{1\%} - D_{99\%}}{D_{Mean}}$$

Dose fall-off was studied using $R_{50\%}$ which was defined as:

$$R_{50\%} = \frac{Volume\ of\ 50\%\ Isodose\ line}{Planning\ Target\ Volume}$$

The differences across planning techniques were evaluated using a 2-tailed paired Student's T-test and the significance was established for a p-value < 0.05.

Results

Tumor volume variation with treatment

In this study, non-coplanar, non-opposing, 3D conformal 6MV photon beams were used with 80% isodose line covering at least 95% of PTV. The treatments are spread across 3-5 days. The fractionation schemes for the 10 patients were as follows: 4 patients – 12Gy×4 fractions, 2 patients – 18Gy × 3 fractions, 1 patient – 20Gy × 3 fractions and 1 patient – 11Gy × 5 fractions. The reduction in tumor volume over the course of therapy was insignificant (p = 0.2 for GTV and p = 0.17 for PTV) as shown in **Figure 2**. Before treatment, the mean volume of the GTV was 11±8 cc (range: 2 – 24 cc) with the corresponding PTV volume of 43±24 cc (range: 12 – 82 cc). At the end of treatment, the GTV changed by 0±25% (range: -33% – 43.5%) and the PTV by 2±15% (range: -20% – 28%), averaged over all the patients. As such, we were not able to observe any detectable change in tumor volume over the course of treatment. The error bars associated with the tumor volumes were derived from the QUASAR™ respiratory motion phantom study.

Comparison between prescription dose, planned dose and the delivered dose

Delivered dose was calculated for all the ROIs and compared with the planned dose. The planned and delivered dose to the OARs including spinal cord, esophagus, lungs and heart were almost identical without any significant differences with p-value > 0.15 on a 2-tailed paired Student's T-test. While the maximum delivered doses to GTV and PTV did not change significantly (<0.1%), the minimum delivered doses to the GTV and PTV deviated by -4±5% and -19±15%, respectively, when averaged across patients over all fractions. When averaged across patients over all fractions, the delivered mean dose to the GTV and PTV deviated from the planned dose respectively by -1 ± 1% and -2 ± 2%, as shown in **Figure 3**. A 2-tailed paired Student's T-test did not reveal the presence of any statistically significant difference between planned and delivered doses to GTV and PTV (p-value > 0.1). The fact that there are small differences between the mean doses delivered and planned to the GTV, we infer that the set-up uncertainties have been adequately compensated via our applied PTV margin.

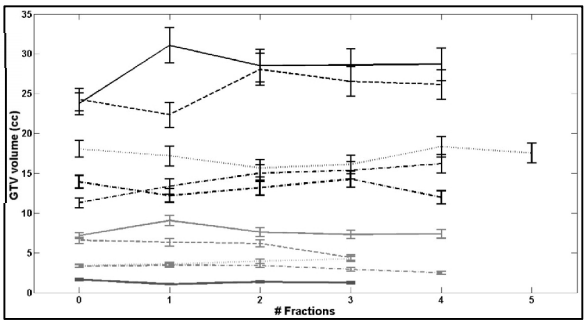

FIG. 2: Variations in the GTV for the ten lung tumor patients during treatment are shown. The GTV for fraction #0 is derived from the pCT whereas the GTV for subsequent treatment fractions was derived from the CBCT. Error bars are derived from a motion phantom study and are 6% and 7% for the pCT and CBCT, respectively.

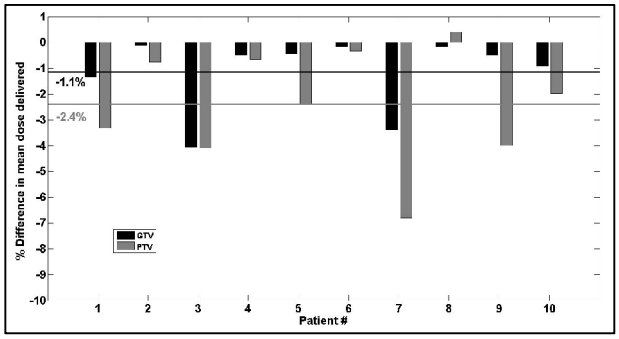

FIG. 3: Distribution of percentage differences between the doses delivered and planned to GTV and PTV are shown along with mean values in black and grey lines, respectively.

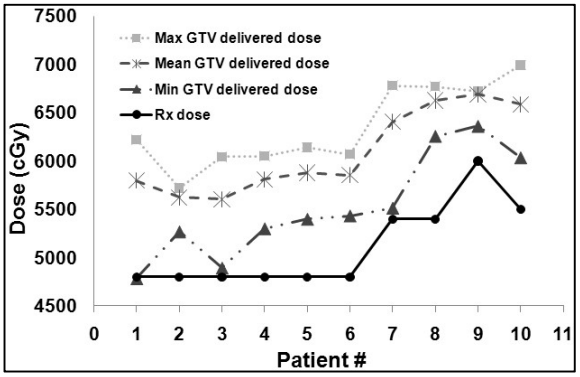

FIG. 4: Prescription radiation dose (Rx) (cGy) as compared with the maximum, mean and minimum GTV delivered dose (cGy) for the 10 patients is shown. In all cases, the delivered dose exceeds the Rx.

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The data presented thus far suggests that GTV excursions within the PTV are minimal and result in only minor dosimetric differences between the planned and delivered GTV doses. The intent of the PTV margin is to ensure dosimetric coverage of the GTV at the prescription isodose level in the presence of geometric excursions. In all the cases analyzed in the study, the contours of GTV from the CBCT images were visually verified to be within the PTV contour in pCT. The mean planned dose to the GTV is, by design, higher than the prescription dose, due to the heterogeneous nature of the dose within the PTV volume, and our practice of prescribing to the 80% isodose line.

In the absence of geometric excursions, the GTV receives a higher dose than it would if it was subject to the random or systematic excursions implied by the application of the PTV margins of 5, 5 and 10 mm along the lateral, anterior/posterior and superior-inferior axes, respectively. In **Figure 4**, we show that the mean dose delivered to the GTV exceeds the prescription dose by 19% on average. On average, the minimum delivered dose exceeds the prescription dose by 8% and the maximum delivered dose by 25%. Data presented thus far, demonstrate the geometric accuracy of dose delivery.

Reduction in the PTV treatment margin

In our first investigation into the feasibility of reducing the volume of irradiated normal tissue, we reduced the PTV margin. However, during the simulation process, we discovered that it was impossible to meet the prescribed dose volume constraints without either increasing the field aperture (i.e., increasing the block margin) or by prescribing to a lower isodose line. In **Figure 5**, we show that the required block margin increased as the PTV margin decreased, ensuring a constant field aperture outside the GTV. For all patients, the PTV_5_5_10 margin required the smallest block margin, whereas PTV_1_1_1 required the largest block margin. Intermediate PTV margins were consistent with this trend, the sum of the block margin and the 3-axes average of PTV margin were constant to within 0.7 mm. This had the net effect of rendering the field aperture (outside the GTV) to be almost constant, regardless of the PTV margin applied. This is illustrated using an example shown in **Figure 1**. Shown in **Figure 1(a)**, PTV_5_5_10 passes the dose-volume constraint (PTV_5_5_10 V95%Rx > 95%) with 0 mm block margin. When PTV treatment margin was shrunk in size, it fails the dose-volume constraint (PTV_3_3_3 V95%Rx < 95%) with 0 mm block margin, but passes (PTV_3_3_3 V95%Rx > 95%) with 5 mm block margin, as shown in **Figures 1(b)** and **1(c)**, respectively. As stated earlier, the field aperture width or the sum total of the block margin and the PTV margin stayed constant to within 0.7 mm for all the 5 test plans. This resulted in very small variation in the volume of tissue covered by the Rx isodose line. Shown in **Figure 6** is the volume of tissue covered by the Rx isodose line (cc) for the 10 patients with Rx dose prescribed to the 80% isodose line (R^2 = 0.40). As expected, the Rx isodose volume scales with GTV, but is not impacted by changes to the PTV treatment margin.

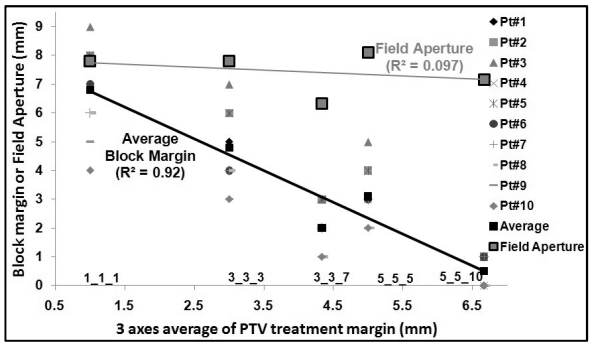

FIG. 5: Block margin (mm) used in creating test plans that met the dose-volume constraint is inversely related with the 3-axes average of PTV treatment margin (R^2=0.92), such that the total field aperture is constant to within 0.7 mm (R^2=0.097). The data was analyzed for the 10 treatment plans with Rx dose prescribed to the 80% isodose line.

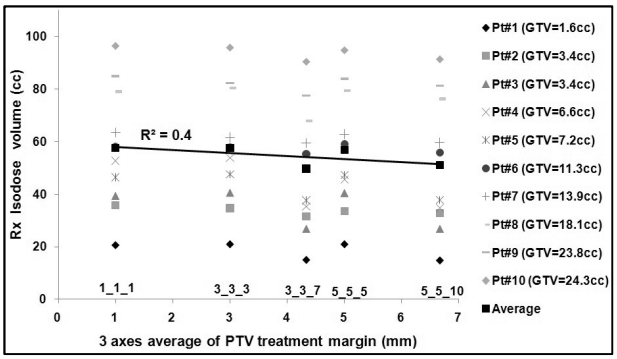

FIG. 6: Plot showing the relationship between the volumes covered by prescription isodose line (cc) and the 3-axes average of the PTV treatment margin (mm) (R^2=0.40), along with volume of gross tumor. The data were analyzed for the 10 treatment plans with Rx dose prescribed to the 80% isodose line.

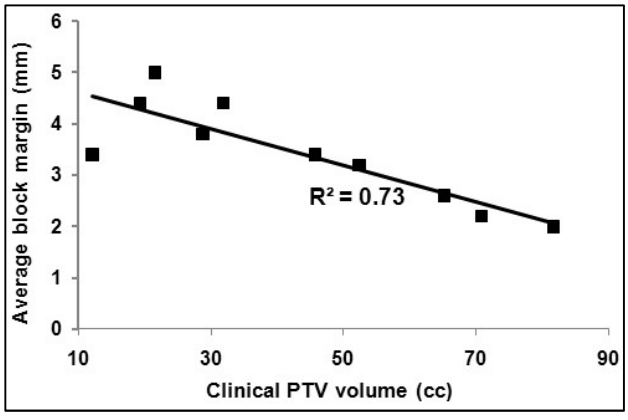

FIG. 7: Plot showing the relation between the volume of clinical PTV (cc) and the block margin (mm) when averaged across the 5 test plans for each of the 10 treatment plans.

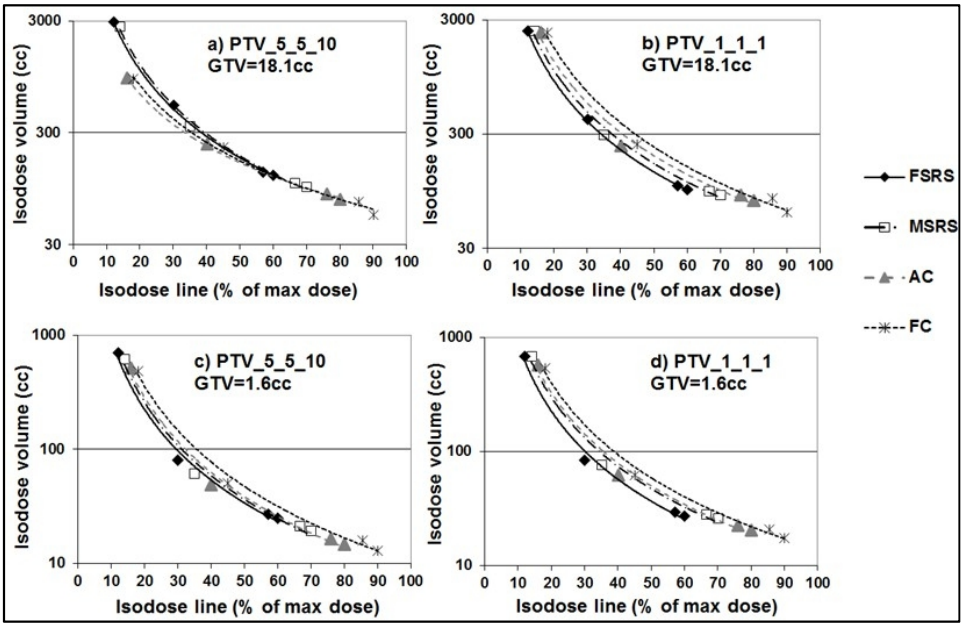

FIG. 8: Plot showing the absolute volume (cc) irradiated by the isodose line (as % of maximum dose) for test plans. a) PTV_5_5_10; b) PTV_1_1_1 in a relatively large tumor (GTV volume = 18.1 cc); c) PTV_5_5_10; and d) PTV_1_1_1 in a relatively small tumor (GTV volume = 1.6cc). The 4 types of prescription techniques used are full SRS (FSRS), moderated SRS (MSRS), aggressive conventional (AC) and full conventional (FC) that correspond to the prescription at 60%, 70%, 80% and 90% of global maximum dose line.

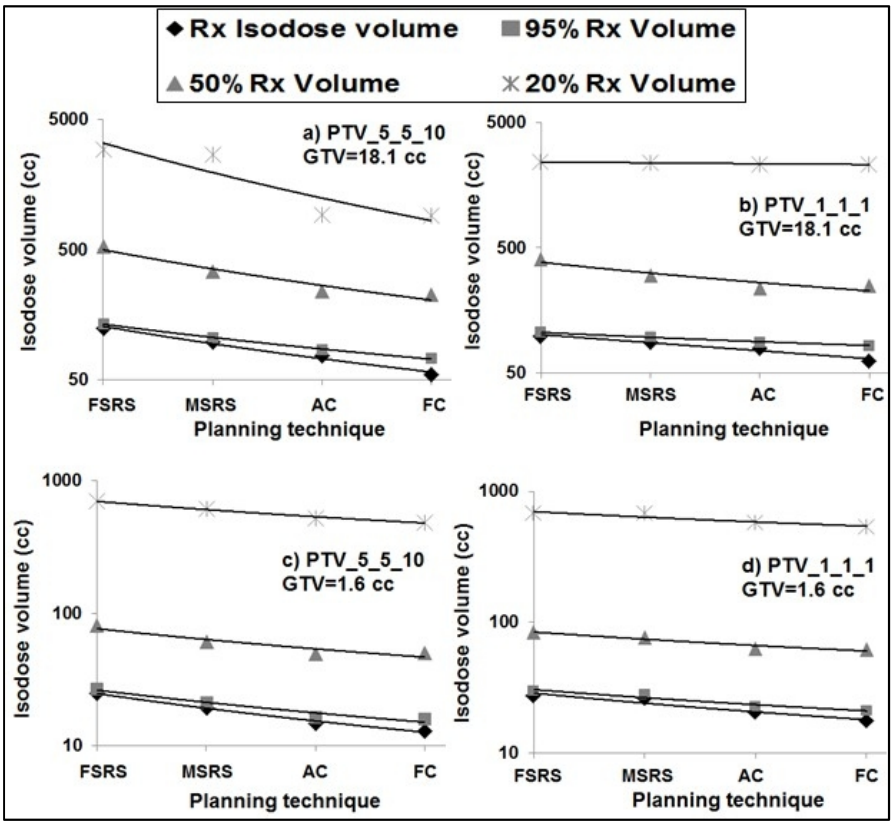

FIG. 9: Volume irradiated by 100%, 95%, 50% and 20% Rx isodose lines (in cc) in a) PTV_5_5_10; b)PTV_1_1_1 in a relatively large tumor (GTV volume = 18.1cc); c) PTV_5_5_10; and d) PTV_1_1_1 in a relatively small tumor (GTV volume = 1.6cc). Notice the uniform decrease in volume of %Rx isodose lines with the more conventional planning strategies than with the stereotactic strategies. Full SRS (FSRS) – 60%, Moderated SRS (MSRS) – 70%, Aggressive conventional (AC) – 80%, and Full conventional (FC) – 90% of the global maximum dose.

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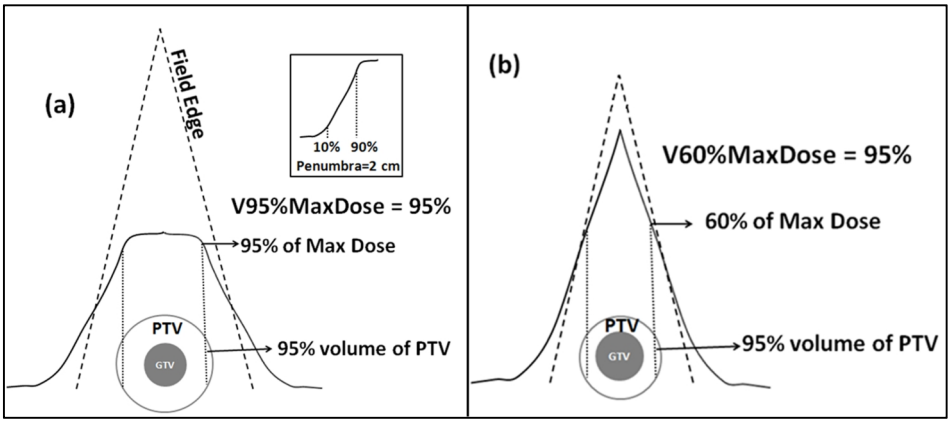

FIG. 10: Plot showing the impact of changing PTV treatment margin and prescription isodose line. In (a) 95% of PTV is covered by the prescription isodose line which is set to 95% of the global maximum dose; (b) 95% volume of a relatively smaller PTV is covered by the 60% isodose line, resulting in a larger global maximum dose and usage of higher monitor units.

A similar trend was seen when comparing the average block margin to the volume of the PTV. The average of the block margins for the 5 test plans showed negative linear correlation ($R^2 = 0.73$, p-value $< 5 \times 10^{-4}$) with volume of the PTV in the treatment plan. This is displayed in **Figure 7**. This is consistent with conventional treatment planning experience, in which the penumbra from the field aperture encompasses a relatively small fraction of the target volume and therefore, smaller block margins may be used for larger PTV while still adhering to the desired dose volume constraints.

Changes to the prescription isodose line

An alternative to increasing the block margin in order to meet the PTV_X_Y_Z V95%Rx > 95% planning constraint, is to prescribe to a lower isodose line. To assess the efficacy of this strategy, we analyzed the absolute volume of tissue irradiated by a certain dose level for varying prescription strategies. **Figure 8** shows that the absolute volume of tissue irradiated by a certain dose level is lowest for the full stereotactic prescription technique (i.e., prescription to the 60% isodose line), and is highest using full conventional prescription techniques (i.e., prescription to the 90% isodose line). This result is a confirmation of the stereotactic strategies, such as Gamma Knife treatments, that typically prescribe to the 50% isodose line in order to achieve a high degree of conformity.

Figures 8a and 8, correspond to PTV_5_5_10 and PTV_1_1_1 test plans of a patient with a relatively large tumor (i.e., GTV volume of 18.1 cc), while **Figures 8c and 8d** correspond to a patient with a relatively small tumor (GTV volume = 1.6 cc). This data confirms the understanding that prescribing to lower isodose levels (i.e., using a stereotactic prescription technique) allows for more conformal treatment and a reduction in the amount of irradiated normal tissue, especially for small tumors and small target margins. Specifically, the difference in the absolute tissue volume irradiated between the techniques is greatest in **Figure 8d** (i.e., small tumor, small margin), and smallest in **Figure 8a** (i.e., large tumor, large margin). However, the difference in the volumes of normal tissue irradiated using the above mentioned prescription techniques are not statistically significant (p-value > 0.1) for the representative case and needs to be studied on a case-by-case basis.

As described above and shown in **Figure 9**, we expected the volume of irradiated tissue to decrease with the more aggressive, or stereotactic, types of plans. However, when we plotted the volume of tissue that received 50% of the prescription dose, rather than 50% of the global maximum dose, the data reveal the opposite trend. That is, the more aggressive, or stereotactic, prescription techniques result in a larger volume of tissue receiving any given absolute dose, as demonstrated in **Figure 9**.

The mechanism responsible for this behavior is the fact that SRS prescription techniques achieve target coverage by increasing the monitor units and accepting higher "hot spots", relative to the prescription dose. Note that this higher global maximum dose irradiates a small region within the PTV, thereby increasing the dose inhomogeneity within the PTV. The large monitor unit settings used in these treatment techniques contribute additional dose across the patient volume, including low and high isodose levels. **Figures 9a and 9b** correspond to PTV_5_5_10 and PTV_1_1_1 test plans of a patient with a relatively large tumor (GTV volume = 18.1 cc), while **Figures 9c and 9d** correspond to a patient with a relatively small tumor (GTV volume = 1.6 cc).

Plan evaluation

The dosimetric parameters (CI, HI and $R_{50\%}$) evaluated for the 60% - 90% prescription isodose line plans were tabulated in **Table 2**. The values represented were mean ± 1 standard deviation. CI values were similar between 60%-70% pre-

scription plans and marginally higher for 80% - 90% prescription plans, but the differences were insignificant (p-value > 0.1). HI values of 60% prescription plan were similar to the 70% prescription plans, but were significantly higher than both 80% and 90% prescription plans (p-values 0.05). $R_{50\%}$ values of 60% prescription plan were significantly smaller than those of the 70% - 90% prescription plans with p-values < 0.05.

TABLE 2: Comparison of planning parameters at 60%, 70%, 80% and 90% prescription isodose lines represented as mean ± 1 standard deviation across patient plans.

	60%	70%	80%	90%
CI	1.20±0.13	1.22±0.1	1.24±0.17	1.28±0.11
HI	0.37±0.05	0.29±0.03	0.22±0.02	0.14±0.02
$R_{50\%}$	3.48±0.23	3.81±0.32	3.93±0.24	4.34±0.32

Discussion

We began this investigation with the goal of assessing whether our treatment techniques accurately delivered the planned tumor dose. The results shown in **Figures 3 – 4** suggest that our immobilization, planning and daily set-up techniques result in good dosimetric coverage of the target volume. Specifically, **Figure 4** shows that all GTVs studied received a mean dose that deviated from the planned dose by less than 4% and that with one exception, all PTVs received a mean dose that deviated from the planned dose by less than 4%. With statistically insignificant differences between the planned and delivered doses to the GTV and PTV, there is likely very little negative clinical impact to the reduced minimum dose to the PTV, since we established that the GTV received the desired dose. An assumption made in the study is that the positional variation following the CBCT acquisition and prior to beam-on is negligible. We note that these results may not translate to different techniques. It is feasible to study the difference between planned and delivered biological effective dose (BED) in SBRT of lung tumor using image guidance and this aspect of radiobiology is not studied here.[14]

Of the possible mechanisms of dose discrepancies between planned and delivered doses, tumor deformation, or growth, were considered. **Figure 2** shows that, for our data, there was not a statistically significant change in the tumor volume, suggesting that tumor growth, or shrinkage, is negligible. The error bars used in this data were derived from a motion phantom study and are 6% and 7% in the pCT and CBCT images, respectively.

Figure 5 and **Figure 6** illustrate that using the traditional approach of reducing the PTV margin can have little impact on the volume of tissue irradiated, especially for smaller tumors. We attribute this to the fact that the small field apertures used in SBRT have a significant portion of their cross sections contained within the penumbra region. The associated steep dose fall off degrades the dose coverage disproportionately for small tumors, requiring an increase in the block margin, as shown in **Figure 7**. A similar trend with rapid fall in the homogeneity index (=maximum PTV dose/Rx dose) with increasing block margin (referred as "beam margin") was seen with the small brain lesions in a stereotactic radiosurgery study (SRS) by Hong *et al.*[15]

We found that the only method by which the volume irradiated by a certain dose level can be reduced is to prescribe to a lower isodose line as shown in **Figure 8**. As indicated in **Figure 9**, this results in an increase in the global maximum dose and the volume of all absolute dose levels. This implies that the renormalization necessarily increases the applied monitor unit settings. The impact of renormalization on the mean dose to the GTV was shown in **Figure 9**. An explanation for this behavior is illustrated in **Figure 10**. Consider a scenario in which a relatively large PTV was targeted using the 95% isodose lines for 95% volume coverage as shown in **Figure 10(a)**. In this case, the aperture width is such that the beam penumbra does not impact the majority of the PTV dose and the dose fall-off outside the PTV is slow. Alternatively, by targeting a relatively small PTV (for the same sized GTV) as shown in **Figure 10(b)**, the beam penumbras begin to overlap due to the small field size. In such a case, there is no homogenous dose region, and the only way to deliver a desired dose to 95% of the PTV is to prescribe to a lower isodose line. In doing so, the global maximum dose increases, as does the absolute dose delivered to the lower isodose lines and the dose fall-off outside the PTV is fast. Lower than 80% isodose line prescription plans might be preferred for tumor control and reduced toxicity.

Plans with 90% isodose line prescription should be limited to cases where dose homogeneity takes priority, an observation shared by Ohtakara *et al.*[16] However, the prescription isodose lines ranged from 70% - 90% in their study making it inadequate to determine if 70% was the most optimal. A recent SRS study on brain lesions had proposed the dose dropping speed concept by fitting the mean dose in multiple rind structures around PTV with a double exponential function of the distance from the PTV surface.[17] An observation made in their study which matched with ours is that a significantly steep dose falloff and better normal tissue sparing was observed in prescribing to 60% - 70% isodose lines than in 90% isodose line especially for smaller tumors. While exploring the wider range of 50% - 90%, the dose dropping speed was found to increase with decreasing prescription isodose line and plateaus at 60% - 70% isodose line.

Dose inhomogeneity within the PTV is considered acceptable and even potentially advantageous. In a phantom study on determining the optimal prescription isodose line for LINAC-based SBRT, it was found to occur between 59% and 69% for lung tumors which is consistent with our findings.[13] This study optimizes for conformity, dosimetric and radiobi-

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ological parameters and minimizes normal tissue irradiation. A Monte Carlo study on SBRT of lung tumor by Widder *et al*. concludes that prescribing to an isodose lower than 80% of the isocenter dose would improve normal tissue sparing.[18] None of the above four studies investigated the effect of altered block margins which we have attempted here.

The 90% plan had the worst CI values compared with 60% - 80% plans, but the values were not significantly different. HI values and mean, maximum PTV dose decreased with increasing prescription isodose line among the 60%-90% plans. $R_{50\%}$ values were shown to be increasing with the prescription isodose line with 90% isodose plans having inferior dose gradient. For all of the plans, values of CI and $R_{50\%}$ agree with the recommended values of RTOG report 0813 within the specified minor deviation. Although CI values were similar across different prescription isodose lines, HI and $R_{50\%}$ values were significantly different in the 60%-70% plans than in the 80%, 90% plans.

The practice of renormalization in conventional treatment planning typically involved prescription isodose lines of 95% - 98% resulting in less than a 5% dose prescription variation across patients and clinics. In SBRT planning, the normal tissue sparing can be improved by the choice of prescribed isodose line in a wider range of 50% - 90%. As the prescription isodose line decreases, the dose heterogeneity within the target increases. In addition, the tolerance of target dose heterogeneity is clinically relevant even for SBRT. Although within the target, the global maximum dose in a low isodose line prescription plan is much higher than in a high isodose line prescription plan. Caution has to be exercised to ensure dosimetric conformity during delivery with precise setup accuracy. The clinical implication of tumor dose heterogeneity and tumor control is poorly understood. Further investigation is expected to improve our understanding of impact that the tumor dose heterogeneity has on tumor control.

Overall, these results indicate that the percentage isodose line specification affect dose distribution both within the target and in the normal tissue when the same prescription dose is administered with same target coverage. Planners should be aware of the significance and the most optimal plan has to be selected on a case basis.

Conclusion

The planning, immobilization and set-up techniques used in our clinic appear to result in set-up reproducibility that results in agreement between planned and delivered mean dose to the GTV to within 2%. The planned and delivered minimum dose to the GTV agreed to within 4%. Tumor volumes are stable during SBRT, to within the error in volume measurement. For the small tumors and target volumes treated with SBRT, we found that traditional margin reduction techniques do not affect a reduction in the volume of tissue irradiated to any absolute isodose value. In this study, plans based on 60%, 70%, 80% and 90% prescription isodose lines with similar target coverage were compared. Prescription to 60% - 70% isodose levels would be beneficial for both tumor control and normal tissue toxicity. These results call for further investigation to determine whether the treatment plans prescribed to lower isodose line can lead to better 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.

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