

## ORIGINAL ARTICLE

**Investigating strategies to reduce toxicity in stereotactic ablative radiotherapy for central lung tumors**

SASHENDRA SENTHI, MAX DAHELE, BEN J. SLOTMAN &amp; SURESH SENAN

*Department of Radiation Oncology, VU University Medical Center, Amsterdam***Abstract**

**Background.** Stereotactic radiotherapy for central lung tumors has a narrower therapeutic index than that for peripheral tumors. Tumor tracking strategies have been proposed to reduce treatment volumes and toxicity, however they need to consider uncertainties in tumor size and shape change throughout respiration to ensure optimal local control. We quantified these uncertainties and explored strategies to account for them. **Material and methods.** Ten patients with central tumors, PTV > 100 cm<sup>3</sup>, motion > 5 mm and a 10-phase 4DCT without significant artifact in the tumor region were evaluated. Uncertainties were quantified using GTV size in different phases, and the Hausdorff distance (HD) between the phase 50% GTV and other phases after soft-tissue rigid registration. An individualized internal target volume for tracking (ITV<sub>T</sub>) was generated from the union of the GTVs in all phases after rigid registration. This was compared to ITVs generated for tracking based on the phase 50% GTV alone or with isotropic margins of 3 or 5 mm for size and volume overlap. **Results.** Median free-breathing PTV size and motion were 162.1 cm<sup>3</sup> (110–210) and 8.9 mm (6.1–14.1). Overall, median GTV size variation and HD were 4.7% (0.2–22.3) and 6.3 mm (3.9–17.6). Tracking using GTV 50% alone resulted in median volume overlap with ITV<sub>T</sub> of 71.7% (range 56.8–85.1). Isotropic margins of 3 or 5 mm always resulted in a volume overlap less than 95% or a volume larger than the ITV<sub>T</sub>. **Conclusions.** Changes in size and shape of central lung tumors are substantial during respiration. These limit the ability to reduce treatment volumes with tracking, especially if isotropic margins are used. An individualized ITV for tracking, such as the ITV<sub>T</sub> is preferred.

Stereotactic ablative radiotherapy (SABR) is the preferred treatment for medically inoperable peripheral early-stage lung tumors [1,2]. In this setting, high rates of local control are achieved and toxicity is infrequent [3,4]. For central tumors there is an increased risk of high-grade toxicity [5], and strategies to mitigate this, include reducing prescribed doses, accepting lower PTV coverage or reducing setup margins [6–9], which may compromise local control.

SABR is widely planned using four-dimensional computed tomography (4DCT), from which it is common to delineate a free-breathing internal target volume (ITV) encompassing the gross tumor volume (GTV) in all breathing phases [10,11]. In addition to motion, this incorporates other uncertainties including variation in tumor size and shape during breathing [12,13]. Strategies that reduce treatment volumes such as tumor tracking [14] may reduce ITV size and therefore the risk of

toxicity [15,16]. However, reported experiences with tumor tracking typically generate plans using a GTV-defined from a single breathing phase, which is then considered the ITV for tumor tracking [17–19]. This resultant ITV no longer accounts for changes in size and shape as a free-breathing ITV would. Instead, additional margins may or may not be added to the ITV for tumor tracking to account for these uncertainties. For large, central tumors, where tumor tracking may have the greatest therapeutic benefit, we quantified these variations in tumor size and shape and investigated different strategies to account for them.

**Material and methods***Study population*

The planning computed tomography (CT) scans from 10 patients with 1) central lung tumors, 2) a

Table I. Baseline tumor characteristics.

		n	%
T-Stage (7th edition)	T2a	4	40%
	T2b	5	50%
	M1	1	10%
Location	Upper thorax	3	30%
	Lower thorax	7	70%
	Left lung	6	60%
	Right lung	4	40%
Central location	Peri-hilar	5	50%
	Para-cardiac	1	10%
	Para-mediastinal (non-cardiac)	4	40%
Size	Median tumor diameter in mm (range)	52.5 (38–65)	
	Median PTV volume in cm <sup>3</sup> (range)	162.1 (110–210)	
Movement	Median motion in mm (range)	8.9 (6.1–14.1)	

PTV, planning target volume.

planning target volume (PTV) greater than 100 cm<sup>3</sup>, 3) tumor motion greater than 5 mm (3D displacement vector of the center of mass), and 4) 10-phase 4DCT visually free of gross artifact in the tumor region (as evaluated by two Radiation Oncologists), were assessed in this retrospective study. Four-dimensional CT images were acquired in uncoached free-breathing conditions without contrast, using a 2.5 mm slice thickness. The clinical free-breathing ITV (ITV<sub>FB</sub>) was defined by the union of the GTVs from all 10 breathing phases [20]. The clinical PTV was generated using an isotropic 5 mm expansion of the ITV<sub>FB</sub>.

#### *Quantifying variation in tumor size and shape during breathing*

By consensus agreement, two Radiation Oncologists delineated the GTV in phase 50% of the planning 4DCT. Using deformable image registration (Velocity AI, version 2.7) this was propagated through the remaining phases and manually edited when required by the same observers [21]. Subsequently, GTV size in each phase relative to phase 50% was determined. Next, after soft-tissue rigid registration of the GTV in each phase with the phase 50% GTV, the Hausdorff distance (HD) [22] was determined.

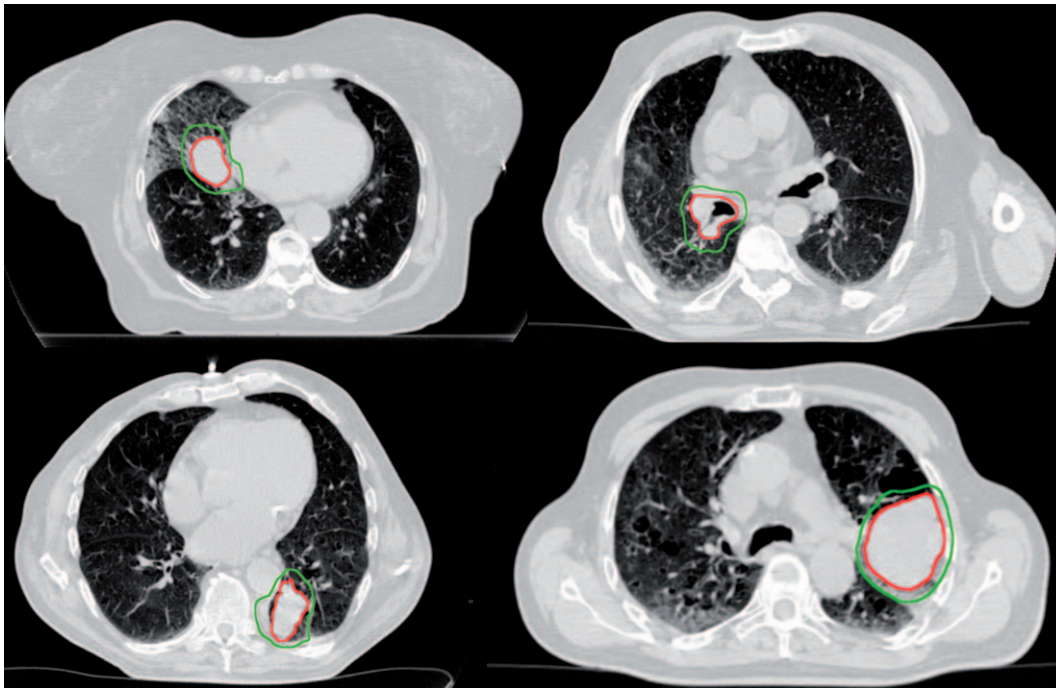


Figure 1. Representative axial slices (phase 50%) of four central tumors included in this study. Top left para-cardiac, top right hilar, bottom para-mediastinal (non-cardiac). The inner and outer outlines define the gross and planning tumor volumes, respectively.

This assumed tracking could be achieved with the same accuracy as rigid registration of static images, thus more effectively enabling size and shape variation to be assessed independent of respiratory motion. The region of interest for rigid registration was the GTV with a margin of approximately 1 cm and included both translations and rotations.

*Impact of variation in tumor size and shape on tracking volume*

Soft-tissue rigid registration of the phase 50% GTV to other individual phases was used to assess coverage by the phase 50% and model the scenario of tracking the GTV 50% without accounting for changes in size and shape in other phases. The union of all GTVs after rigid registration with the phase 50% GTV was referred to as the individualized

tracking ITV ( $ITV_T$ ). This tracking aperture was considered to account for variations in tumor size and shape during breathing. In addition, the following tracking strategies were also assessed, with respect to their size and volume overlap with  $ITV_T$ . All analyses were carried out at the ITV level since we were interested in whether or not this structure adequately reflected variation in size and shape: 1) Phase 50% GTV alone [17–19]; 2) Union of phase 50% and 0% GTVs after rigid registration ( $ITV_{0+50}$ ); 3) Phase 50% GTV + 3 mm isotropic margin [12]; and 4) Phase 50% GTV + 5 mm isotropic margin.

*Statistical considerations*

Descriptive statistics were used for all baseline characteristics. Average size differences relative to phase 50% were based on absolute differences (i.e. all

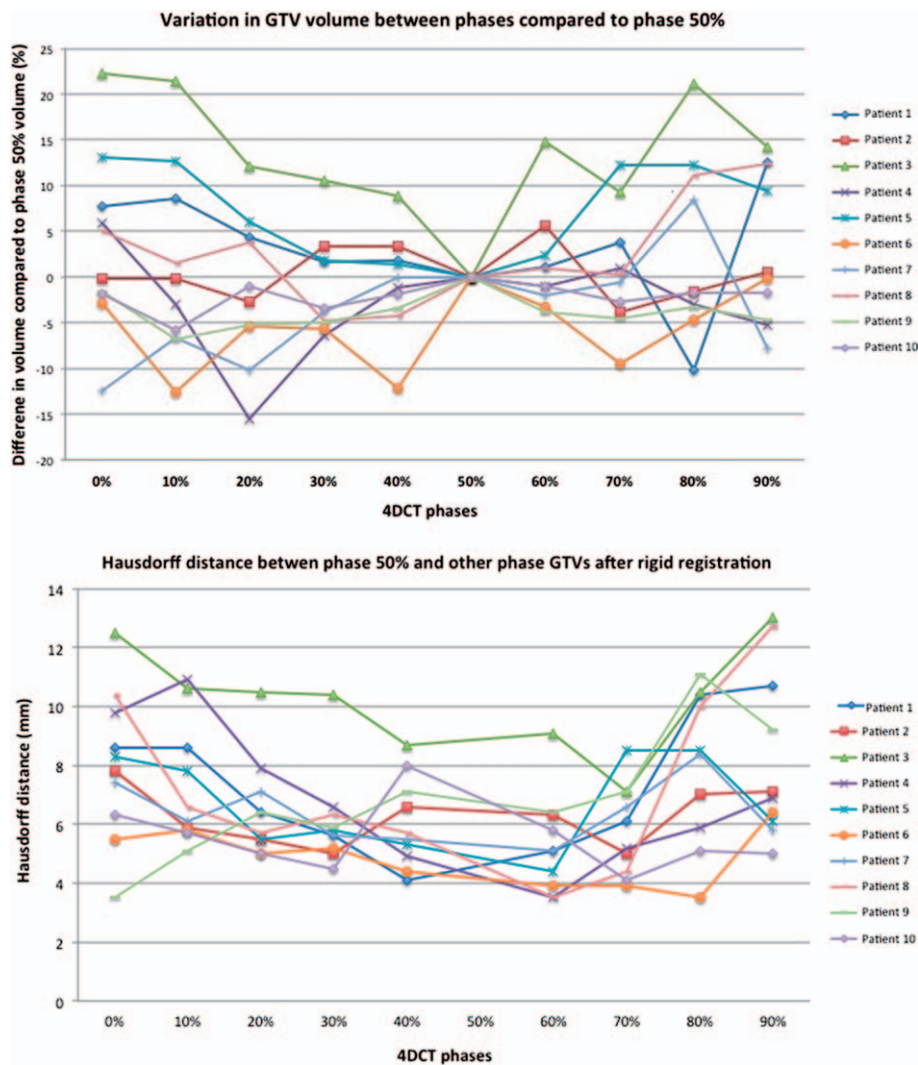


Figure 2. Differences in gross tumor volume (GTV) size during breathing relative to phase 50% GTV (above), and the maximum Hausdorff distance between the GTV in each respiratory phase and the GTV 50% (below). Shown in color online.

values were considered positive for this analysis). All statistical analyses were performed using Statistical Package for Social Sciences (version 18.0).

## Results

Baseline tumor characteristics are summarized in Table I. Representative axial slices of four cases illustrating the types of tumors studied are shown in Figure 1. The median tumor diameter, PTV size and tumor motion were respectively, 52.5 mm (range 38–65), 162 cm<sup>3</sup> (range 110–210) and 8.9 mm (range 6.1–14.1).

Overall, GTV size varied a median of 4.7% (range 0.2–22.3) while the median maximal GTV size variation from phase 50% for individual patients was 12.5% (range 5.6–22.3). GTV size did not correlate with respiratory phase, and the volume of the phase 50% GTV could be the largest (patients 6 and 9) or the smallest (patients 3 and 5) (Figure 2). Overall, the median HD relative to GTV 50% was 6.3 mm (range 3.9–17.6). The HD exceeded 5 mm for more than half the breathing cycle in all patients (Figure 2). Figure 3 shows the phase 0% and 50% GTVs for patient 3, who had the greatest change in GTV size and shape with respiration.

A tracking volume generated using the GTV 50% alone, resulted in a median volume overlap of ITV<sub>T</sub> of 71.7% (range 56.8–85.1). Using the union

of GTV 50% and 0%, improved this to a median 82.1% (range 79.5–89.4). Tracking volumes generated using the phase 50% GTV with an isotropic margin of 3 or 5 mm, resulted in volume overlap of less than 95% or volume larger than ITV<sub>T</sub> (Table II). ITV<sub>T</sub> was smaller than the ITV<sub>FB</sub> by a median 8% (range 2.1–21.2).

## Discussion

The importance of an adequate SABR dose for optimal local control has been confirmed in several studies [5,7,8]. However, despite the use of respiratory tracking, concerns about toxicity when treating central tumors with SABR, have necessitated deliberate PTV under-dosing or dose reduction in a substantial proportion of patients, resulting in a measurable impact on local control [6]. The findings in our study suggest that in some patients, marked variation in tumor size and shape may also influence local control and that trying to account fully for this would compromise the reduction in treatment volume that can be achieved with tracking. This suggests that tracking alone may not be an adequate solution for safer SABR delivery in very central tumors.

Our main finding was that overall, GTV size and shape varied by approximately 5% and more than 5 mm, respectively. We also observed that an ITV based on the GTV in a single respiratory phase or the

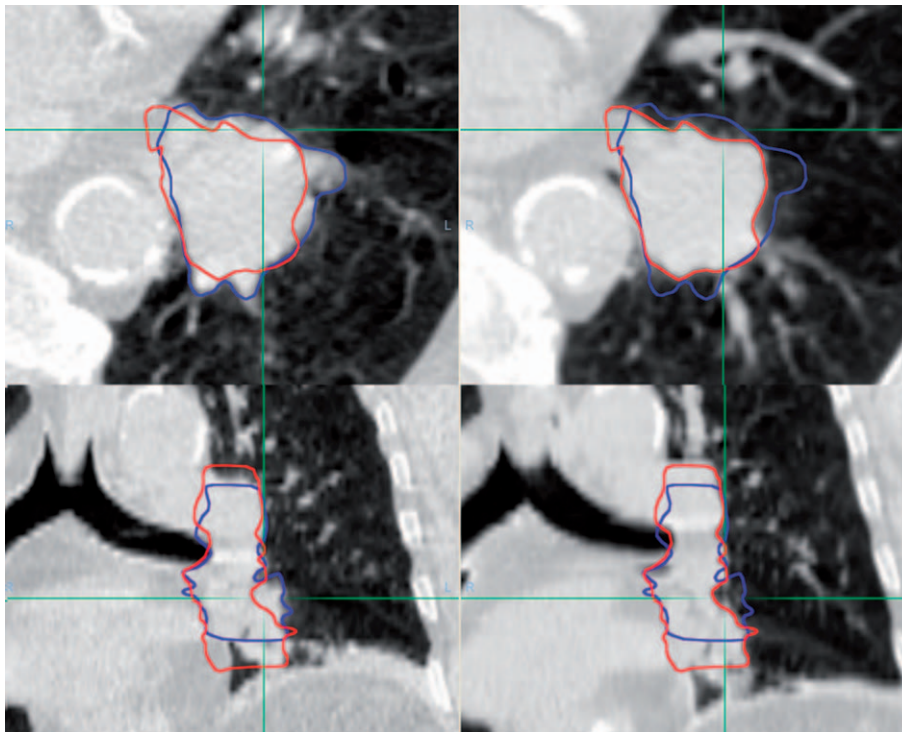


Figure 3. Illustration of significant variation in size and shape during breathing, with representative axial and coronal slices from patient 3 whose tumor showed the greatest change. CT images on left from phase 50% and on right from phase 0%. Contours from both phases are shown after rigid registration of the CT scans.

Table II. The impact of strategies to account for change in tumor size and shape during breathing.

	ITV <sub>FB</sub> (cm <sup>3</sup> )	ITV <sub>T</sub> (cm <sup>3</sup> )		GTV 50% alone	GTV 50% + 3 mm	GTV 50% + 5 mm	GTV 0% and 50%
Patient 1	111.8	97.7	Size (%)	64.1	91.7	123.2	79.5
			Coverage (%)	64.1	82.6	93.1	79.5
Patient 2	85.8	81.5	Size (%)	72.6	109.6	149.9	81.3
			Coverage (%)	72.6	95.2	99.5	81.3
Patient 3	104.1	101.9	Size (%)	56.8	84.1	113.5	78.5
			Coverage (%)	56.8	76.0	86.8	78.5
Patient 4	89.7	86.4	Size (%)	70.1	107.3	146.9	79.5
			Coverage (%)	70.1	89.1	96.2	79.5
Patient 5	64.9	62.4	Size (%)	69.6	105.8	146.2	89.4
			Coverage (%)	69.6	89.4	97.4	89.4
Patient 6	66.9	52.7	Size (%)	79.9	115.7	156.9	87.7
			Coverage (%)	79.9	96.0	99.8	87.7
Patient 7	53.1	43.8	Size (%)	78.5	118.0	174.2	82.9
			Coverage (%)	78.5	96.3	99.5	82.9
Patient 8	65.3	56.1	Size (%)	70.8	106.1	145.1	80.0
			Coverage (%)	70.8	92.0	97.9	80.0
Patient 9	106.8	96.0	Size (%)	82.0	109.0	138.8	86.0
			Coverage (%)	82.0	96.6	99.8	86.0
Patient 10	117.3	110.4	Size (%)	85.1	109.8	144.3	90.1
			Coverage (%)	85.1	97.9	100.0	90.1

The free-breathing ITV (ITV<sub>FB</sub>) is defined by the union of gross tumor volumes (GTVs) from all 10 4DCT phases and represents an ITV that accounts for motion and the changes in tumor size and shape during breathing. The union of GTVs after rigid registration (ITV<sub>T</sub>), accounts for variation in tumor size and shape only, assuming motion is perfectly accounted for using a tracking strategy. The size and coverage of the ITV generated using other strategies have been reported relative to ITV<sub>T</sub>.

extremes of respiration alone is generally inadequate to account for these variations. Applying an isotropic margin of 3 or 5 mm to the phase 50% GTV did not completely account for variations in size or shape, or it resulted in an ITV that was larger than ITV<sub>T</sub>. These results suggest that such variations limit the ability to reduce treatment volumes with tracking, particularly if isotropic margins are used to account for them. Despite this however, we found that the ITV<sub>T</sub> was smaller than the ITV<sub>FB</sub> by a median 8% confirming that accounting for size and shape variation with the ITV<sub>T</sub> when using a tracking strategy, may still offer gains over free breathing treatment.

Although there are methodological differences, our findings are consistent with previous reports. Wu et al. considered the extremes of breathing alone and found patients tumors > 80 cm<sup>3</sup> (n = 3) all had a HD > 10 mm [13]. Lu et al. found an additional 3 mm isotropic margin was required to account for variations in size and shape if coverage by the 95% prescribed isodoses was desired [12]. However, this only considered the extremes of respiration and we observed that a 3 mm isotropic margin frequently generated an ITV larger than the ITV<sub>T</sub>. Using manual contours in all 4DCT phases, Persson et al. reported maximal GTV size variation was a median of 15.1% (range 2.3–90.8) [23], while we observed a maximal variation of 12.5%.

We acknowledge that while tracking is the topic of interest in this study, gated delivery is more frequently

employed in routine clinical practice as a strategy to minimize toxicity. Gating enables target volume reduction and accounts for changes in tumor size and shape with breathing, and the degree to which it might reduce toxicity depends on the relative location of the tumor and OAR during the gating phases.

A primary limitation of this study is the fact that our results are based on manual contours, which are subject to contouring uncertainties. We tried to limit these by having two clinicians contour by consensus and using deformable image registration to propagate contours over remaining phases, which has been shown to improve consistency [21]. It is unclear how much of the total variation in size and shape during breathing we observed can be attributed to deformation or imaging artifact. However, we deliberately selected patients with no gross 4DCT artifact in the tumor region and variations in size and shape were not maximal in the mid-respiratory phases as would be expected if they were largely due to imaging artifacts [11,23]. We also acknowledge that changes in the size and shape of organs-at-risk, baseline shifts in tumor position and irregular breathing patterns impact tracking strategies, however a detailed analysis of the impact of these factors was beyond the scope of the current study for reasons including a lack of multiple 4DCT datasets. The HD is a very sensitive metric, as it uses pixel-level information representing the single largest of the shortest surface-to-surface distance measures between the GTV volumes being compared.

Although it has been used by other authors [13], the HD may overestimate the clinically relevant variation in size and shape, and the margin required to account for such changes. For this reason, size and overlap were also assessed. Additionally, the accuracy of rigid registration used to reflect the tracking may have influenced the HD results. Finally, a dosimetric analysis has not been performed to determine the clinical significance of these target volume differences.

The reduction in target volume using tumor tracking for large, central tumors appears to be limited by changes in tumor size and shape during breathing. In some patients, accounting for these with the  $ITV_{T_3}$  results in a smaller high-dose target volume than the  $ITV_{FB}$ . Although using the  $ITV_{T_3}$  merits further investigation as one strategy to reduce the toxicity of central lung SABR without compromising local control, where underlying tumor-OAR geometry remains unfavorable its impact may be limited.

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