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Original Article

An evaluation of the mid-ventilation method for the planning of stereotactic lung plans

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ABSTRACT

Background and purpose: Stereotactic ablative body radiotherapy for lung plans requires 4DCT. Most radiotherapy centres use this to determine an internal target volume (ITV), despite studies suggesting that planning on a mid-ventilation (Mid-V) phase can reduce target volumes. The purpose of this study is two-fold: to determine whether the Mid-V approach provides adequate coverage and to discuss methods to enable the Mid-V approach to be applied more widely.

Method: 4D scans of 79 patients were outlined on every phase. The mid-V phase was identified. Margins were determined from the range of motion, and plans generated with a 55 Gy prescription. A grid-based method was used to get the probability of tumour coverage in the presence of systematic and random uncertainties, with and without blurring for breathing motion.

Results: For the Mid-V plans with the margins calculated from the van-Herk formula, after blurring doses for breathing, the coverage (dose covering 95% of the CTV 95% of the time) was greater than for plans with isotropic 5 mm margins uncorrected for breathing (58.2 Gy v 57.3 Gy). Similar results were obtained for a linear margin chosen as 0.15 of the breathing range. Deformable contour propagation in a commercial outlining system (ProSoma) identified the same mid-V phase in the majority of cases.

Conclusion: Our results confirm that a mid-V approach can be used to reduce the PTV size, with no loss of tumour coverage. We propose the use of a simplified margin formula equal to the margin ignoring breathing plus 0.15 of the range of motion.

Practice varies between radiotherapy departments with respect to the method used to account for breathing motion within the planning target volume (PTV). Where information on breathing motion is available in the form of a 4D-CT, there are two conflicting approaches. One approach is to define an internal target volume (ITV) [1] that covers the clinical target volume (CTV) in all phases of the 4D-CT, and to add margins to this, covering the non-respiratory geometric uncertainties. Although ICRU [1] defines the ITV in relation to the CTV, in cases where no margin for sub-clinical spread is required this is equivalent to covering the Gross Tumour Volume (GTV) in all phases of the 4D-CT. The other approach is to define the GTV on a single phase: either a Mid-Ventilation (Mid-V) image chosen as the phase nearest to the time-weighted geometric centre of the motion [2,3], or a Mid-Position (Mid-P) image created by deforming all the phases to produce a single image representing the time-weighted position of all the images [4].

The ITV method effectively treats the breathing motion as a systematic motion, adding the full extent of the motion to the margin. The Mid-V and Mid-P method treats the breathing motion as a random error, which can be combined in quadrature with other random margins when calculating the PTV margin. This means that the ITV approach generally results in larger treatment volumes than the Mid-V or Mid-P approach.

A recent study of clinical practice found that the majority of radiotherapy centres use the ITV method, with only 6% of centres using the Mid-V or Mid-P method [5]. There are two main reasons for the slow uptake of the Mid-V or Mid-P approach. One is that methods for determining Mid-V phase (or generating the Mid-P image), and for estimating the standard deviation of breathing motion, are not generally available outside a small number of centres. The other is a belief that breathing motion, being very non-gaussian, cannot be combined with other random motions, and that this approach will lead to underdosing of tumours [6].

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The purpose of this study is two-fold: to determine whether the Mid-V approach provides adequate coverage of target volumes, and to discuss methods that can be used to enable the Mid-V approach to be applied more widely in departments without access to non-commercial software.

Methods

The study used 4DCT scans of patients who had been treated with SABR for lung cancer. Data were used from 76 patients, 3 of whom had had two courses more than a year apart, giving 79 datasets. All the patients had been treated according to UK guidelines for lung SABR [7]. In each case an ITV had been drawn (to cover the tumour in all phases of the 4DCT in a movie-loop), and grown isotropically by 5 mm to produce a PTV.

The 4DCT was acquired on Toshiba/Canon Aquillon scanners (Canon Medical Systems, Otawara, Japan) equipped with either the Varian RPM system or the Varian RGSC system (Varian, Palo Alto, USA), and binned typically into 10 or 11 phases, equally spaced by time. For the purpose of this study, the gross tumour volume (GTV) was outlined in ProSoma (MedCom, Darmstadt, Germany) on each phase. A MatLab programme was used to determine the centre of mass of each GTV. The mean of these positions gave the time-weighted centre of mass; the phase in the exhalation part of the cycle closest to this time-weighted average was identified, and designated as the mid-V phase. For each phase the displacement of the centre of mass relative to the centre of mass of the mid-ventilation GTV was calculated (in x, y, and z). This set of positions was stored as a kernel (of ten equally weighted positions). Fig. 1 illustrates the use of this kernel. We assume that moving the target relative to the beam is equivalent to moving the beam relative to the target, and that dose is shift invariant. The top element of Fig. 1 shows the ten isocentre positions (note that two of them near the origin are almost superimposed). The middle two elements show the dose distribution (in a sagittal plane) before and after summing ten shifted dose distributions. The lower two elements show dose profiles through the centre of the tumour in the AP and SI directions. It can be seen that although the shifts in the SI direction go beyond 7 mm, the shifts (at the 55 Gy dose level) are 1.3 mm on one side, 1.8 mm on the other. The superposition is done in three dimensions – in this illustration the range of left–right motion was considerably smaller than in the other directions.

The range of motion was calculated by subtracting the minimum from the maximum for each of the three coordinates of the centre of mass.

Margins

The van Herk formula for the CTV–PTV margin [8] gives

$$Margin = 2.5\Sigma + \beta\left(\left(\sigma^2 + \sigma_p^2\right)^{0.5} - \sigma_p\right) \quad (1)$$

where Σ is the standard deviation of systematic uncertainties, σ is the standard deviation of random uncertainties, σ_p is the parameter of the Gaussian defining the penumbral width, and β is a parameter that depends on the isodose chosen to surround the PTV. For the SABR plans produced, for a prescription of 55 Gy the maximum dose was required to be between 59.4 Gy and 75.6 Gy, meaning that the prescription isodose was between 72.7% and 92.6%. For 92.6%, [8] gives $\beta = 1.46$. We used $\sigma_p = 5.5$ mm [9]. Setting $\Sigma = \sigma = 1.83$ mm gives a margin of 5.0 mm. No margin was applied for sub-clinical spread, hence CTV = GTV. This formula assumes we wish to ensure a minimum dose to the CTV of at least the prescription isodose, for 90% of patients, and excludes rotational errors and shape deviations.

For the plans produced on the Mid-V phase, the range A was used to estimate the standard deviation of breathing motion $\sigma_{br} = 0.36$ A [10]. The margin formula then became:

$$Margin = 2.5\Sigma + \beta\left(\left(\sigma^2 + \sigma_{br}^2 + \sigma_p^2\right)^{0.5} - \sigma_p\right) \quad (2)$$

Calculated margins were rounded up to a whole number of mm in the Left–Right and Anterior–Posterior direction, and to a multiple of the slice spacing (3 mm) in the Superior–Inferior direction.

Planning

VMAT plans were produced in Pinnacle, using a scripted semi-automated class solution based on a clinical method. The plans were produced using 6MV x-rays, for PTVs using the Mid-V GTV plus 5 mm, and for PTVs using the margin calculated using equation (2). The UK SABR consortium guidelines [7] were followed: the aim was to ensure that at least 95% of the PTV received the prescription dose of 55 Gy, and that at least 99% of the PTV received 90%. The maximum dose within the PTV was between 59.4 Gy and 75.6 Gy.

Analysis method

For each of the plans, the probability distribution of CTV coverage was calculated using the software tools described by [11] to calculate the dose covering 99% of the CTV for a range of geometric uncertainties. A grid-based method was used to sample a probability density function, using a two-step method to simulate random errors (with a σ of 1.83 mm) and systematic errors (with a Σ of 1.83 mm). From the distribution of dose values, the value that would be obtained in at least 95% of simulations was recorded.

This calculation was performed twice for each plan, once for the original dose distribution exported from the planning system, and once using a dose distribution that had been blurred by convolving the dose distribution with the breathing kernel described above. The results for the blurred plan, with margins either from Eq. (2) or linear margins, were compared with those for the unblurred plan with 5 mm isotropic margins. If no reduction is observed, this indicates that the margin is ample to cover breathing uncertainties.

Deformable propagation of outlines

Since the manual outlining of all ten phases of a 4D-CT is very labour intensive, we investigated an alternative method using deformable-registration tools available in a commercial outlining system, ProSoma. The manual outlining on bin-3 was used as the basis for propagation to all the other 4D bins. The methods described above were used to determine the range and to identify the mid-V bin. The results were compared with the results derived from the outlines manually delineated by an oncologist on all phases.

Results

The mean and standard deviation of the range of motion was 1.9 mm ± 1.1 mm in LR, 3.2 mm ± 2.0 mm in AP and 5.3 mm ± 4.7 mm in SI. The largest range observed in each direction was 6.3 mm, 10.6 mm and 22.2 mm respectively, giving Mid-V to PTV margins of up to 6 mm, 7 mm and 15 mm respectively. SI saw the largest motion in 41 patients (51%), AP in 31 patients (39%) and LR in 8 patients (10%).

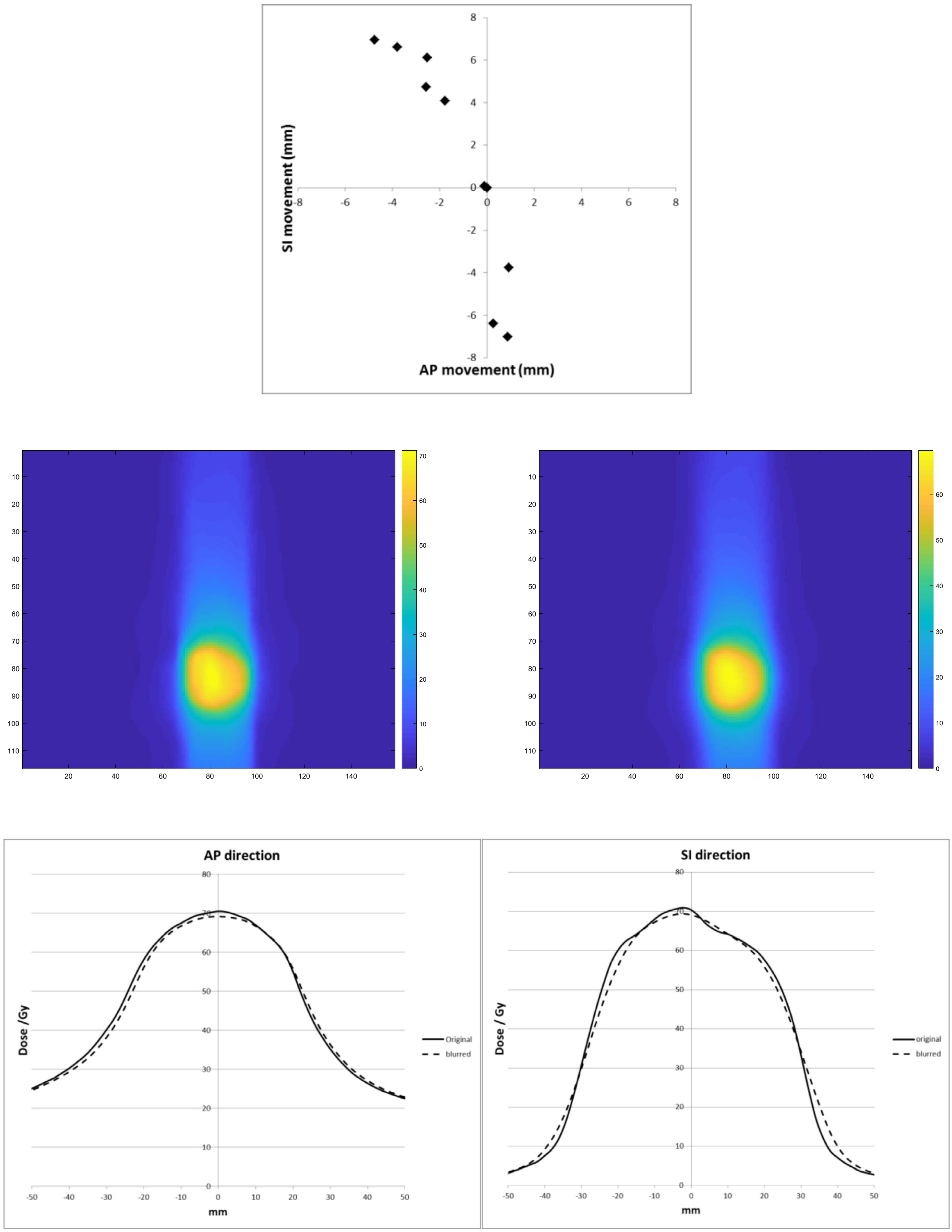

Fig. 1. The top panel shows the positions of the centre of mass of the 10 bins, relative to the central bin (third dimension not shown). The two middle panels show coronal dose distributions; the unblurred is on the left, the blurred (by superimposing doses shifted by the values in the top panel) is on the right. The bottom two panels compare dose profiles in the two cardinal axes for the blurred and unblurred distributions.

Fig. 2 shows the distribution of which of the exhalation phases is closest to the time averaged tumour position. Although phase 3 is the most frequent, the majority are on other phases.

When ignoring breathing motion, the plans on the Mid-V phase with 5 mm isotropic margins had on average 57.3 Gy covering 99% of the CTV at least 95% of the time. Fig. 3 shows the distribution of

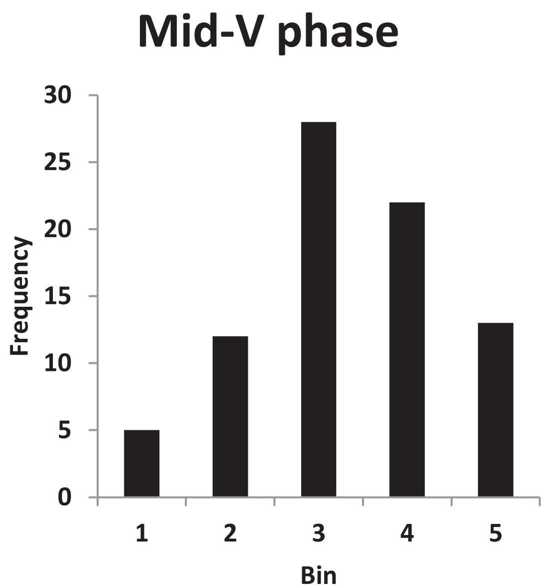

Fig. 2. Histogram showing the distribution of bins identified as the mid-V phase.

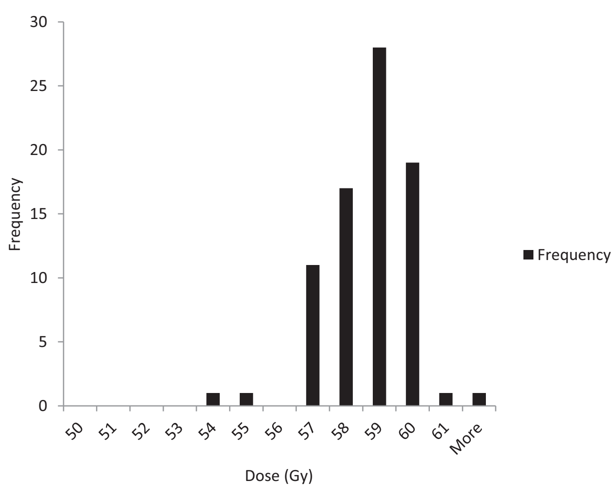

Fig. 3. Distribution of doses covering 99% of the CTV at least 95% of the time, for plans with 5 mm isotropic margins, ignoring breathing motion.

these results. For 74/79 cases, this value was greater than or equal to the 55 Gy prescription dose. When the same plans were analysed with the inclusion of breathing motion, the mean fell to 56.8 Gy. In 55 cases, the result for the blurred dose was lower than for the original plan; in 29 cases it was lower by >1%.

For the plans with the margins calculated with Eq. (2), and analysed with breathing motion, on average 58.2 Gy covered 99% of the CTV at least 95% of the time. Fig. 4 shows the distribution of these results. In 74 cases (94%) this dose exceeded that for the original plan without inclusion of breathing. In 3 cases it was lower by less than 1%. In 2 cases it was lower by >1% (1.8% and 4.0%). The one that was 4% lower had the second largest Ant-Post motion range (9.9 mm), however the one with the largest Ant-Post range did not show any issues.

Following the same reasoning as is used to simplify the second term of Eq. (1) to 0.7 σ, it is possible that wider acceptance of the concept of use of a mid-V may result from simplifying the effect of

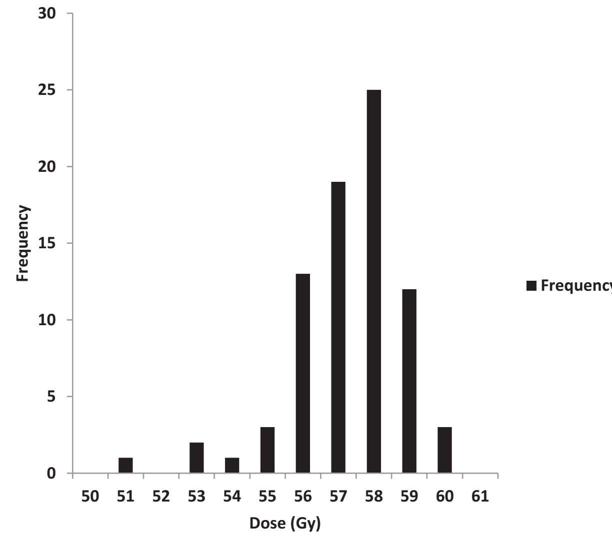

Fig. 4. Distribution of doses covering 99% of the CTV at least 95% of the time, for plans with margins calculated with Eq. (2), and analysed with breathing motion.

breathing motion to a linear margin. Fig. 5 shows the increase in margin required for breathing (Eq. (2)-Eq. (1)) and a linear approximation of 0.15 the range.

Combined with the effects of rounding, this linear margin gives identical results to the full equation for the vast majority of patients. 73/79 would have the same margin, 4/79 would have a margin too large by 1 mm (or 3 mm in Sup-Inf as a result of rounding to a whole slice spacing). In the two cases with the largest Sup-Inf range the linear formula gives a margin 3 mm smaller than Eq. (2). However in both these cases, plans produced using the linear formula have a dose covering 99% of the CTV at least 95% of the time that exceeds that for the static plan, suggesting that the linear formula gives adequate margins in both these cases. This was sufficient for the range of motion studied (up to 22.2 mm), but may not be valid for larger ranges of motion.

To test the suggestion of [6] that blurring would not work if all the motion was at the extremes of its travel, we recalculated one patient (with ranges of 2.3 mm, 5.7 mm and 14.0 mm in LR, AP and SI respectively), using a modified breathing kernel in which all the positions were replaced with either of the extreme values for that direction. With the original kernel, the blurred plan on the margins determined above gave a dose (covering 99% of the CTV at least 95% of the time) that was 102.0% of that in the static plan. For the modified kernel this reduced to 99.6%, which was still clinically acceptable. This demonstrates that breathing traces do not give all the doses at the extremes, but even if they did the methods described would still work.

The deformable propagation takes 6–10 minutes in ProSoma. This compares to the time for an oncologist to outline on each phase, which took 20–60 min per patient. Exporting the structure sets takes an additional 6 min.

Fig. 6 shows the range determined from outlines deformably propagated in ProSoma (based on manual outlining on a single bin) with the range determined by the reference method of manually outlining on all bins. In the vast majority of cases the range of motion determined by propagation was within 2 mm of the range determined from manual outlining of each phase.

Fig. 7 shows the residual error defined as the distance between the centre of mass of the phase chosen as mid-V, and the average centre of mass of all the oncologist-delineated outlines. In 50/79 cases the mid-V phase identified by both methods is the same. In 29/79 cases it differed. The change was generally by 1 bin, although

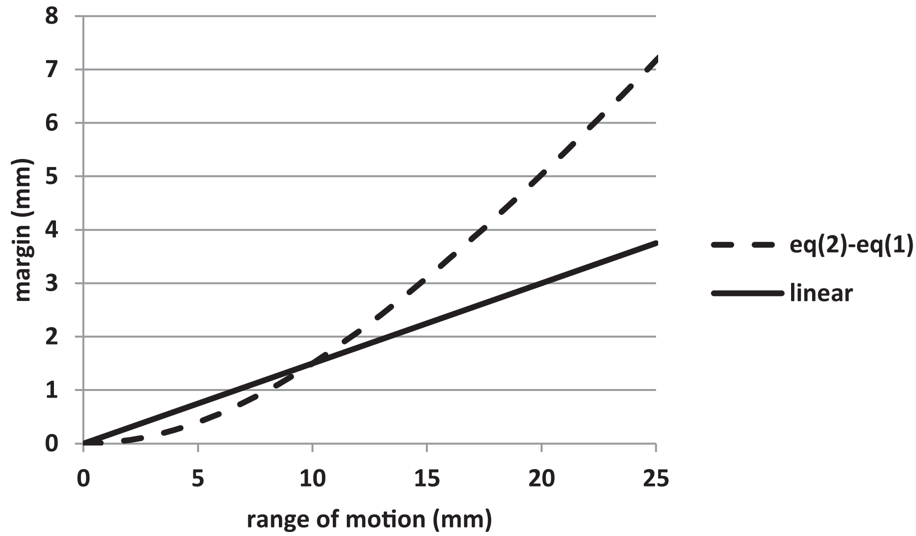

Fig. 5. The increase in margin required for breathing (the difference between the margins of Eq. (1) and Eq. (2) (dashed line) and a linear approximation of 0.15 the range (solid line).

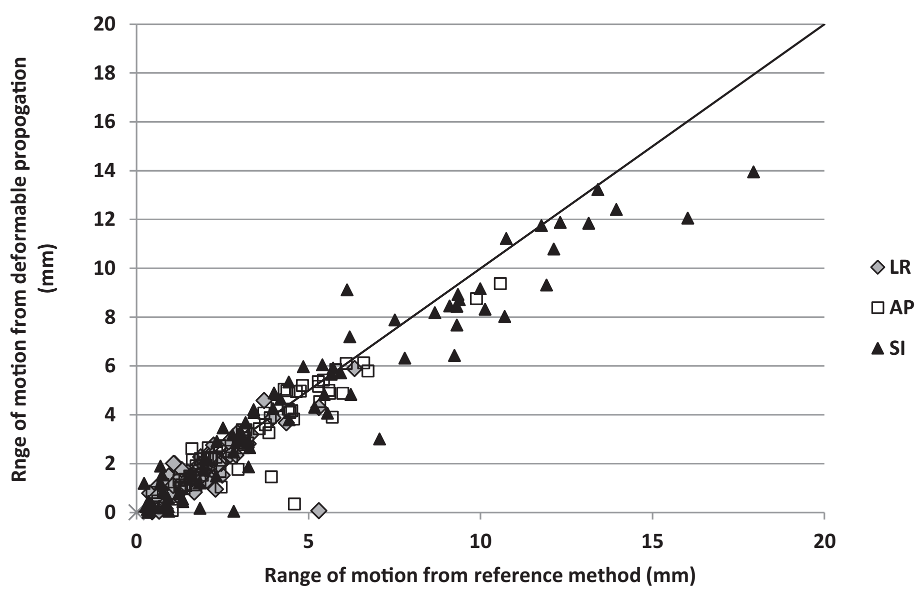

Fig. 6. The range determined from outlines deformably propagated in ProSoma (based on manual outlining on a single bin), compared with the range determined by the reference method of manually outlining on all bins.

in two cases (where the range of movement was very small) a change of 4 bins was seen, without changing the residual error by more than 1 mm. Since the oncologist-defined outlines are taken as the "ground truth", the residual errors for this will be the smallest possible; hence all the residual errors from the propagated outlines will either be the same as these (where the same bin is found) or greater (where another bin is found). The largest change in residual error corresponded to a bin change of 1 for a patient with a large range of motion.

Fig. 8 compares the SI extent of PTVs calculated using an ITV with the SI extend of PTVs calculated using a Mid-V method. The former are the length of a volume which encompasses all the phases, grown by 5 mm/5 mm/6 mm in the RL/AP/SI directions. The latter are the length of the Mid-V phase only, grown by the margins determined in Eq. (2). Fig. 8 shows that in all cases the length of the Mid-V based PTV is less than or equal to the length of the ITV-based PTV. The mean length of the Mid-V based PTV is 30.9 mm, compared with 34.6 mm for the ITV-based PTV.

Discussion

These results are in agreement with the results of [2–4] that volumes constructed from the Mid-V phase, with the addition of a margin determined by Eq. (2), provide adequate coverage in the presence of breathing motion. The diameter of an ITV will exceed that of a single phase by approximately equal to the range A, whereas the increment from the method described here is approximately 0.3A. Hence the diameter of the PTV to gain adequate coverage will be smaller than those used clinically by approximately 0.7A, which on average is 3.8 mm in SI. This reduction is confirmed by the results in Fig. 8. Changing to a Mid-V based approach would reduce the volume of normal lung irradiated, with no diminution in tumour coverage.

Given these advantages, the question arises as to why there has not been widespread adoption of the mid-V or mid-P methods, and that the ITV method remains the one most commonly used clinically [5].

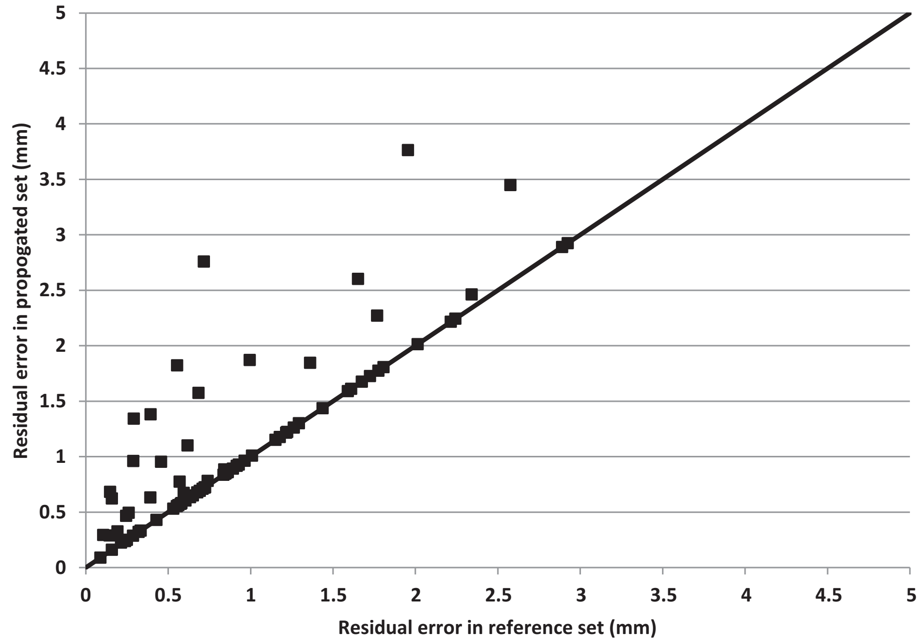

Fig. 7. The residual error, defined as the distance between the centre of mass of the phase chosen as mid-V, and the average centre of mass of all the oncologist-delineated outlines. Where a point falls on the line it indicates that the same bin has been chosen by both methods, and hence has the same residual error.

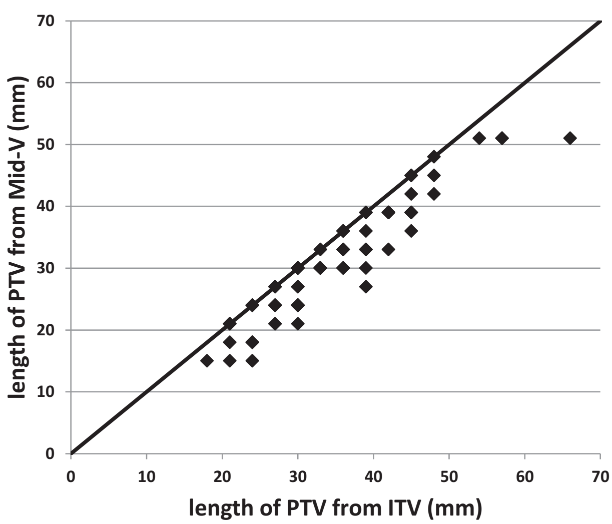

Fig. 8. The length of the PTV derived from the Mid-V phase with the addition of the margin from Eq. (2), compared with the length of the PTV derived from the ITV with 5 mm isotropic margins. In all cases the length of the former is less than or equal to the length of the latter.

One possible reason is a perception that the method does not provide adequate coverage. McKenzie [6] argued that the shape of breathing motion meant that most of the time was spent at the two extremes of the motion, and that therefore the only way to ensure adequate coverage was to extend the margins to cover the full range of breathing. However simulations, including those described here, have shown this not to be the case. Whilst more phases are near the extremes than in the middle, the effect of convolving with the other random errors (especially the penumbra) means that a very non-Gaussian kernel still acts to blur the dose as assumed in the analysis of random errors.

A second reason is the lack of availability of commercial software systems for determining the Mid-V or Mid-P images. All published methods relied on in-house software solutions, or on a combination of commercial and open source software [12]. Delineating on all 10 phases is not something most oncologists have the time to do in routine clinical practice. As a result, most oncologists prefer to delineate an ITV, since this can be done without the need to draw on every phase. For a mid-V method to become practicable, it is therefore necessary to be able to determine which single phase should be used. Nygaard et al [13] looked at a number of alternative methods of doing this. They compared visual evaluation of tumour displacement, rigid registration of tumour position, diaphragm displacement in the CC direction, and carina displacement in the CC direction. They concluded that the first two of these methods were the most accurate. The method of visual examination is the easiest one to implement in a department, using the standard tools for viewing the phases in a treatment planning system. Visual inspection can also be used to get an accurate estimate of the range of motion.

Another possible method, where accurate deformable registration tools exist, is to draw on one phase and deformably propagate to the other phases [14]. Our results show that this method, within a commercial outlining system (ProSoma) can give good results. However the use of this system does not completely remove the need to develop in-house software, since there is still a need to identify the centre of mass of each phase, and choose the phase nearest to the time-weighted average centre of mass.

A possible third reason for the lack of adoption of the mid-V/mid-P methods is that the calculation of the margins using Eq. (2) is not intuitive for many oncologists, who prefer a linear formula, as evidenced by the popularity of the version of Eq. (1) with a 0.7 σ. For this reason we propose the following simplified formula:

$$\text{Margin with breathing} = \text{Margin without breathing} + 0.15 \times \text{range of motion} \quad (3)$$

As shown in the results section, this formula usually gives the same results as Eq. (2), and, in the cases where it does not, it still ensures adequate tumour coverage. Eq. (2) may overestimate the required margin, since the value of $\beta = 1.46$ was chosen for the extreme range of the possible prescription isodoses. At the other end of the range (72.7%), β would become <0.84. leading to smaller margins. However with inverse planned VMAT the ratio of the prescription dose to the maximum dose is unknown at the point of growing the PTV, so a conservative value was chosen.

Since margins between ITV and PTV are typically quite small in SABR, some clinicians may feel uneasy about switching to a Mid-V method that usually makes target volumes even smaller. However if there is a wish to increase the margin for non-breathing uncertainties, this should be done explicitly, rather than relying on the use of an ITV to deliver an extra margin that is dependent on the range of breathing motion. Adding unnecessary margin risks causing toxicity to normal lung [15]. There is increasing evidence that larger primaries (Stage IB ie T2a) also benefit from SABR [16]; for these larger tumours using a mid-V method to limit the size of the PTV will be especially helpful.

A limitation of both the ITV method and the Mid-V method is the assumption that the pattern of breathing at the time of treatment is the same as at the time of the planning 4D CT. The use of 4D cone beam CT for image guidance can detect the cases where the amplitude on the treatment machine is greater than at planning, and ensure that the patient is set up on the correct Mid-V position. However baseline changes during treatment [17] will not be corrected by either of these methods. Breath hold, gating or tracking methods are alternatives where this is an issue [18]; however the residual errors of some tracking systems can lead to needing greater margins than for free breathing.

In this study, we used CT slices obtained at 3 mm slice spacing, and rounded up our margins to a multiple of 3 mm. Potentially slightly smaller PTVs would be obtained in we were to scan in 1 mm slices, since the rounding would add less extra margin. However this would increase the imaging dose, and would increase the outlining time for the oncologist.

The grid-based method used in this analysis assumes shift invariance. This has been shown to be a good approximation when the PTV does not extend into a build-up region [19]. In the lungs, the density of the lung (and hence the penumbral broadening) will vary between breathing phases; since as many phases will be higher as are lower, this is not expected to make a major change to the results.

Conclusions

Planning on a mid-ventilation phase, with margins chosen that treat breathing as a random motion, provides adequate coverage of the tumour, whilst treating less normal lung than would be treated using an ITV.

There is a need for the identification of the mid-V phase (or the generation of a mid-P image) to become standard features in commercial planning systems, or in the 4D-software of CT scanners. Ideally these should also identify the range and calculate the margins. Whilst the identification of the Mid-V phase requires locally developed solutions, most oncologists will continue to delineate ITVs (using features that are built in to commercial planning systems), resulting in larger PTVs than necessary.

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