Evaluation of PTV margins and plan robustness for single isocentre multiple target stereotactic radiosurgery

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ARTICLE INFO

Keywords:
Plan robustness
Single isocentre for multiple targets stereotactic radiosurgery (SIMT-SRS)
Geometrical uncertainty
Planning target volume (PTV) margins

ABSTRACT

Purpose: Robustness to residual setup errors and linac delivery errors of BrainLab Elements single-isocentre-multiple-target stereotactic radiosurgery was evaluated.

Methods: Residual setup errors of 13 patients were evaluated. Linac delivery error was quantified through multi-metastases-Winston-Lutz measurements. PTV margins were calculated using the van Herk recipe. Patient scans were translated and rotated by the median and 95th percentile of the combined uncertainties, and plans were recalculated subsequently. Previous patients’ plans were then replanned with the derived margins, effects on GTV coverage and normal brain doses were assessed.

Results: Mean (±stdev) coverage of all targets in the original plans were 99.4% (±0.9%) and 98.9% (±1.0%) for 1 and 3-fraction patients respectively. Median geometrical errors did not result in significant differences. A statistically significant reduction in coverage to 91.4% (±10.4%) and 93.0% (±9.6%) was seen under 95th percentile errors. Applying the derived optimal margin of 0.5 mm resulted in 78% of the GTVs retaining a global dose increases varied according to the number of metastases.

Conclusions: Plans were shown to be robust to average geometrical uncertainties despite targets having no margins, however occurrence of GTV under-coverage increased under 95th percentile scenarios. The margin was proven to substantially improve the target dose coverage with limited change to local normal brain doses, although not all sources of geometrical uncertainty were considered.

1. Introduction

Stereotactic radiosurgery (SRS) treatments can achieve ablative doses with both high conformity and spatial accuracy to small targets [1]. To minimise the risk of complications from using such high doses, the volume of healthy tissue being irradiated is typically limited by using small or even no gross tumour volume (GTV) to planning target volume (PTV) margins [2]. Historically 1–3 lesions would be treated using either dedicated SRS platforms such as Gamma Knife or using cones with an individual isocentre for each lesion on a linac. Treatment of multiple lesions has become commonplace since non-inferiority of SRS without whole brain radiotherapy has been shown for up to 10 lesions [3]. More efficient linac techniques employing a single isocentre for multiple targets (SIMT) have been developed to enable to treatment of multiple metastases (mets) [4,5]. Through the use of multiple non-coplanar arcs, SIMT plans compare well to multiple isocentre plans with improved normal tissue sparing and gradient indices [6]. The use of SIMT could, however, result in rotational errors having a more pronounced effect on the geometrical treatment accuracy [7–9], with errors potentially increasing with the target’s distance from the isocentre. The importance of correcting both translational and rotational patient setup errors through the use of image-guided radiotherapy (IGRT) together with a 6 degrees-of-freedom (DOF) couch has been shown [10] but small residual setup errors especially when combined with inherent linac delivery error could still be of concern.

A 2018 benchmark of SRS centres in England showed all Gamma Knife and most Cyberknife centres apply no GTV-PTV margin when treating multiple metastases, whereas most linac centres apply a 1 mm margin [11]. The Gamma Knife use of zero margin maybe in part due to the use of frames that are surgically fixed to the skull. Frames have gradually been replaced by frameless thermoplastic face masks for patient immobilization because of their non-invasive nature [12], whether...
the zero margin approach can be translated to these newer forms of treatments remains to be seen [13]. While using no margin may reduce the risk of brain necrosis, a strong correlation between risk of radiation necrosis and normal brain (brain excluding GTV) V12 Gy doses have been seen [14], several papers have recommended adding a margin for SIMT treatments to ensure adequate dose coverage to metastases [8,15].

The aims of this study were, therefore, to derive an optimal margin for SIMT SRS at our centre and to evaluate plan robustness to residual setup errors and linac delivery error with and without this optimal margin.

2. Materials and methods

2.1. Patient cohort and treatment information

In this single centre study, data was analysed retrospectively from patients who had given consent for their data to be used for research purposes. Patients were treated using a SIMT-SRS technique, comprising of multiple dynamic conformal arcs, delivered over 4 to 5 couch angles. Plans were created in the BrainLab Elements treatment planning system and delivered on a Varian linac. Treatments consisted of either: 1-fraction, with 24, 21, 20 or 18 Gy isodose; or 3-fractions, with 24, 21 or 18 Gy prescription isodoses. Radiobiologically equivalent global normal brain dose constraints of V12 Gy < 10 cm³ and V19.5 Gy < 10 cm³ were used for 1 and 3 fraction treatments respectively, additional clinical discretion was applied when constraints could not be met. Since 3-fraction treatments will be subject to inter-fractional variations whilst single fraction does not, analyses were conducted for these two groups of patients separately. The BrainLab ExacTrac system was used for image guidance. It integrates a kV X-ray imaging system, an infrared based positioning system and a 6DOF couch [16]. Prior to delivering the fields at each couch angle, patients were imaged and shifts that were greater than a tolerance limit of 0.5 mm and 0.5° would be applied. Repeated imaging and shifting would occur until the couch corrections were within the tolerance.

2.2. Residual setup error

Residual setup errors were quantified from residual uncorrected translational and rotational shifts. Both the translational deviation and the translational displacements resulting from rotational deviations were calculated for each tumour.

2.3. Linac delivery error

Linac delivery error was assessed via a Winston-Lutz test which measures the coincidence between the treatment and imaging/mechanical isocentres [18]. Weekly measurements were performed using
A multi-metastases-Winston-Lutz (MMWL) Cube from Sun Nuclear Corporation, which has 6 ball bearings within the phantom to mimic multiple metastases. Separate Winston-Lutz tests were performed for each ball bearing. Coordinate system used for this study, as well as the arrangement of ball bearings in the phantom can be found in Fig. 1.

During the test the phantom was first positioned, using the lasers, to the mechanical isocentre (see Fig. 2). Two orthogonal kV-kV images were then acquired using the ExacTrac imaging system. Marker matching were performed at each couch position. Each beam was imaged using the electronic portal imaging device (EPID) of the linac. Exactrac imaging and marker matching were performed at each couch angle. The analytical software then derived the deviation of the ball bearing positions from the MLC defined field centre with trigonometrical relationships based on a modified method from Low et al. (1995) [19] in order to reveal any delivery errors [20].

2.4. Margin derivation

The van Herk margin recipe, stated in Eq. (1) [21], was used to determine the PTV margin m, based on the measured random and systematic components of the residual translational setup errors, the residual rotational setup errors, the linac delivery error, as well as the measured penumbral width (σp) and coverage isodose, which in turn determines the value of β. The combined random (σ) and systematic (Σ) errors are given by Eqs. (2) and (3). The parameter α was set to 2.5 to give a 90% confidence level that the PTV is covered by the intended treatment isodose.

\[ m = \alpha \Sigma + \beta \sigma_p \]  
\[ \Sigma^2 = \Sigma_{\text{translation}}^2 + \Sigma_{\text{rotation}}^2 + \Sigma_{\text{tech accuracy}}^2 \]  
\[ \sigma^2 = \sigma_{\text{translation}}^2 + \sigma_{\text{rotation}}^2 + \sigma_{\text{tech accuracy}}^2 + \sigma_p^2 \]  

Targets were grouped according to distance from isocentre in 2 cm radial bands, and margins were derived separately for these groups to assess whether the target distance from isocentre affects the required margin. Penumbral measurements were obtained from clinical plans of previously treated patients. The penumbra was calculated using Eq. (4)

\[ \sigma_p = \frac{d_{100} - d_{95}}{\text{CGF}_1 - \text{CGF}_{50}} \]

2.5. Plan robustness and quality evaluation

To investigate the effect of geometrical uncertainties on patients, the patients’ CT scans were transformed based on the combined quantified errors resulting from residual setup errors and linac delivery errors. It was assumed that all individual errors follow a one-dimensional Gaussian distribution. If the distribution of residual setup errors had a mean and SD of f(x) and μx, whilst those of delivery errors were f(x) and μy respectively, then the combined error distribution would have a mean and SD of μx + μy and \( \sqrt{\sigma_x^2 + \sigma_y^2} \). When evaluating the effect of these geometrical uncertainties on patients, their scans were subjected to two sets of transformation:

- Median values to represent the nominal scenario
- Median ± 1.64SD (whichever gave a larger shift value) to give a near worst-case scenario corresponding to the 95th percentile \( (\sqrt{1.64^2 + 1.64^2 + 1.64^2} = 2.84) \) of the overall three-dimensional Gaussian distribution error distribution, it represented the largest error that could potentially be experienced by 5% of all targets

Patients’ CT scans were transformed translationally and rotationally using 3D Slicer (version 5.0.3) [23]. The planning CT was then re-registered with the transformed CT using Eclipse treatment planning system (version 16.01.10) and the contours were transferred. The recalculation of doses to these CT scans was performed in Elements (version 3.3.0.379) and dose volume statistics were extracted.

Dosimetric parameters were evaluated in both the original clinical plans and the plans subjected to the effect of geometrical uncertainties to assess robustness. The dosimetric parameters were the target dose coverage and global normal brain doses:

- Percentage volume of GTV covered by the prescription dose, aimed to be 98% or above at our centre
- For 1 fraction patients, volume of normal brain receiving 12 Gy aimed to be < 10 cm³
- For 3 fraction patients, volume of normal brain receiving 19.5 Gy aimed to be < 10 cm³

Statistical tests were then performed to see whether the original, median and 95th percentile groups differed significantly from one another in terms of target dose coverage and dose to normal brain. Since the data was not normally distributed, the non-parametric Friedman’s analysis of variance (ANOVA) was employed for comparing the paired data followed by Dunn’s multiple comparison test as the post-hoc test. Correlations between the target dose coverage and both target-isocentre distance and target volume was analysed using Pearson correlation coefficient. All p-values were corrected for multiple comparisons, with p-values below 0.05 deemed statistically significant. These tests were
performed using the software Statistical Product and Service Solutions (SPSS, version 27.0.1).

Target dose coverage and normal brain doses, both global and local in this case, were also evaluated with and without the application of margins through replanning patients. Local normal brain was assessed by reviewing the dose to a 1 cm annulus around the GTV. If dose bridging occurred between two mets the local normal brain was considered for the summed area:

- For 1 fraction patients, local normal brain receiving 12 Gy aimed to be < 5 cm³.
- For 3 fraction patients, local normal brain receiving 19.5 Gy aimed to be < 5 cm³.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean and SD of residual setup errors for 1-fraction and 3-fraction patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Translations (mm)</td>
<td>Rotations (°)</td>
</tr>
<tr>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>1-fraction Mean</td>
<td>-0.02</td>
</tr>
<tr>
<td>SD</td>
<td>0.17</td>
</tr>
<tr>
<td>3-fraction Mean</td>
<td>0.04</td>
</tr>
<tr>
<td>SD</td>
<td>0.19</td>
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</table>

<table>
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<tr>
<th>Table 2a</th>
<th>Systematic and random residual setup errors for 1-fraction and 3-fraction patients.</th>
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<tr>
<td>Σtranslation (mm)</td>
<td>σtranslation (mm)</td>
</tr>
<tr>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>1-fraction</td>
<td>0.10</td>
</tr>
<tr>
<td>3-fraction</td>
<td>0.08</td>
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<table>
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<tr>
<th>Table 2b</th>
<th>Systematic and random residual rotational setup errors in 2 cm radial bands from isocentre.</th>
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<tr>
<td>Radial band (cm)</td>
<td>N metastases</td>
</tr>
<tr>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>1-fraction</td>
<td>0 – 2</td>
</tr>
<tr>
<td>2 – 4</td>
<td>16</td>
</tr>
<tr>
<td>4 – 6</td>
<td>25</td>
</tr>
<tr>
<td>6 – 8</td>
<td>23</td>
</tr>
<tr>
<td>0 – 2</td>
<td>4</td>
</tr>
<tr>
<td>2 – 4</td>
<td>9</td>
</tr>
<tr>
<td>4 – 6</td>
<td>12</td>
</tr>
<tr>
<td>6 – 8</td>
<td>7</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Mean and SD of translations and rotations from MMWL measurements.</th>
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</thead>
<tbody>
<tr>
<td>Translations (mm)</td>
<td>Rotations (°)</td>
</tr>
<tr>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>Mean</td>
<td>0.20</td>
</tr>
<tr>
<td>SD</td>
<td>0.12</td>
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</tbody>
</table>

Fig. 3. Systematic (left column) and random rotational error (right column) for a) 1-fraction patients and b) 3-fraction patients per target, error bars are included in the 3-fraction patient plots to show the deviation in errors across the 3 fractions per target.
3. Results

3.1. Patient background information

Residual errors for 13 previously treated patients (8 1-fraction patients with a total of 65 metastases and 5 3-fraction patients with a total of 32 metastases) had been analysed for this study. The metastases were grouped by 2 cm radial bands for deriving margins subsequently.

3.2. Residual setup error

Mean and SD of both translational and rotational residual setup errors can be found in Table 1, the number of metastases, resultant systematic and random errors in each radial band can be found in Table 2. The rotational errors were also analysed as a function of target-isocentre distance as shown in Fig. 3. This shows a very weak positive correlation between the magnitude of the error and the GTV distance from isocentre, along with a low $R^2$ for a linear model.

3.3. Linac delivery error

A total of 20 weekly measurements had been performed with the MMWL phantom, results have been summarized in Table 3 and 4. Likewise the errors had been analysed as a function of target-isocentre distance, linear regression was performed and no strong relationship was observed between the error and target-isocentre distance (see Fig. 4).

3.4. Margin derivation

The median prescription dose was 80.7% of the maximum dose to target, the 80% isodose level was therefore deemed close enough to be used in subsequent calculations. The penumbra was determined using the distance between 80% and 50% isodose curves (see Eq. (5) [22]). The median penumbra of all targets was 2.4 mm.

$$\sigma_p = \frac{d_{80\%} - d_{50\%}}{0.84}$$  (5)

An 80% prescription dose to maximum dose level corresponded to a $\beta$ value of 0.84, $\alpha$ was chosen to be 2.50 corresponding with a 90% confidence level [21]. The PTV margins resulting from the measured geometrical uncertainties are shown in Fig. 5, which shows the margin value to generally increase with the distance from isocentre. However, since Elements is only capable of growing margins in steps of 0.5 mm, 0.5 mm was deemed to be the optimal margin to be applied to all targets in this study.

3.5. Plan robustness and quality evaluation

The median and 95th percentile of the overall geometrical uncertainties combined used to assess plans robustness can be found in Table 5.

i. Target Dose Coverage

The percentage of the GTV volume covered by the prescription dose in 1 and 3-fraction patients is shown in Fig. 6 for the original plan, the plan recalculated on the CT transformed with the median error, and again with the 95th percentile error. Table 6 shows target dose coverage from the original plan and under the different patient transformations. Statistically significant differences in target coverage were found between some of the transformations, as shown in Table 6. Mean ($\pm$SD) coverage of all targets in the original plans were 99.4% ($\pm$0.9%) and...
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98.9% (±1.0%) for 1-fraction and 3-fraction patients respectively. Applying median geometrical errors did not result in any significant differences. However, a statistically significant reduction in target coverage to 91.4% (±10.4%) and 93.0% (±9.6%) was seen under 95th percentile errors.

ii. Normal Brain Dose

Fig. 7 shows the normal brain doses under the three transformation scenarios. Friedman’s ANOVA indicated no significant difference in normal brain dose between them for both 1-fraction patients (p = 0.325)
and 3-fraction patients (p-value = 0.549).

iii. Target-Isocentre Distance & Target Volume

The effects of both target-isocentre distance and target volume on the target dose coverage for 1-fraction and 3-fraction patients are illustrated in Fig. 8. Statistical analysis showed limited correlation of target dose coverage with target-isocentre distance and metastases volume, as shown in Table 7.

iv. Margin Application

The prescription dose coverage to targets in original clinical plans is compared to that under different geometrical uncertainties. Applying the derived optimal margin of 0.5 mm resulted in 78% of the GTVs retaining a coverage of 98% or above even in the presence of 95th percentile errors, compared to only 30% if no margins were applied (see Fig. 9).

Results from replanning patients with 0.5 mm margin can be found in Fig. 10. No significant difference to the local normal brain dose was observed, while the global dose increased variably depending on the number of metastases in patients. Generally, the more metastases the patient had the greater the rise in global dose.

Table 7
Correlation of target prescription dose coverage with target-isocentre distance and target volume for 1-fraction and 3-fraction patients.

<table>
<thead>
<tr>
<th></th>
<th>Original</th>
<th>Median</th>
<th>95th Percentile</th>
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<tbody>
<tr>
<td>1-fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance</td>
<td>Pearson coefficient 0.041</td>
<td>0.058</td>
<td>−0.284</td>
</tr>
<tr>
<td></td>
<td>Significance 0.739</td>
<td>0.636</td>
<td>0.019</td>
</tr>
<tr>
<td>Volume</td>
<td>Pearson coefficient −0.317</td>
<td>−0.261</td>
<td>0.122</td>
</tr>
<tr>
<td></td>
<td>Significance 0.009</td>
<td>0.032</td>
<td>0.322</td>
</tr>
<tr>
<td>3-fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance</td>
<td>Pearson coefficient −0.038</td>
<td>−0.167</td>
<td>−0.273</td>
</tr>
<tr>
<td></td>
<td>Significance 0.837</td>
<td>0.361</td>
<td>0.131</td>
</tr>
<tr>
<td>Volume</td>
<td>Pearson coefficient −0.337</td>
<td>−0.027</td>
<td>0.211</td>
</tr>
<tr>
<td></td>
<td>Significance 0.060</td>
<td>0.884</td>
<td>0.246</td>
</tr>
</tbody>
</table>

Fig. 8. Effect of target-isocentre distance and metastasis size on prescription dose coverage for a) 1-fraction and b) 3-fraction patients, the red line indicates the targeted 98% coverage and grey line indicates 100%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
4. Discussion

The primary aim of this study was to evaluate the robustness of SIMT SRS plans towards residual setup and linac delivery errors, and to determine the optimal PTV margins accordingly. In order to do this: residual setup and linac delivery errors were quantified; correlation of the measured errors with target-isocentre distance and target volume was investigated; van Herk margin recipe [21] was used to derive the theoretical GTV-PTV margin; the impact of measured errors and also derived margins on patient dosimetry were assessed.

Minimising geometrical uncertainties is crucial for the implementation of SRS which requires high geometric accuracy and precision to deliver high doses to a localized area. For the sources of uncertainties considered, a single PTV margin was found to be suitable for each GTV in SIMT SRS, regardless of GTV-isocentre distance. This was because both the residual setup and linac delivery errors were found to be small in nature, in the order of submillimeter. Perhaps counterintuitively, only a weak correlation was found between target-isocentre distance and residual setup errors, whilst a moderate correlation with linac delivery errors was found. These findings contradicted other studies that assumed any rotational errors would directly quantify into an additive translational error [8,24], whereas in practice they depended on the position of targets and the axes of rotation about which a displacement occurs. Without quantifying uncertainties from actual clinical data, the errors investigated in these studies might not be clinically relevant.

Simulating the measured systematic errors within the treatment planning system showed that the errors did not pose any statistically significant impact on normal brain dose in both nominal and near worst-case error scenarios. Nor were there any statistically significant changes in target dose coverage for average errors. This showed that the clinical plans are robust to average geometrical errors, even without any margins. Under near worst-case scenario, i.e. 95th percentile error, the target dose coverage was substantially worse than the expected coverage based on the original treatment plan DVH without introduced errors. It should be noted that here the 95th percentile error represented the largest error that could potentially be experienced by 5% of all targets. Since it was not possible to know which, if any, GTVs experienced this degree of error, the displacement was applied to all patients and GTVs to get a near worst case scenario estimate, although it is important to note that this would give an overestimation of the potential impact of geometrical uncertainties.

The correlations of target dose coverage to both target-isocentre distance and target volume were investigated in the presence of different degrees of geometrical uncertainties. Only weak correlations were found in all cases, again contradicting findings in some other studies [8,25]. This may be in part due to the fact that dose was being recalculated when the errors were applied, unlike the other studies which relied on the static dose cloud approximation when determining the impact of errors. The effect of geometrical uncertainties will be dependent on the direction of the error with respect to each beam, for instance rotational errors along the same axis as the treatment arc may have less effect on the dose coverage than rotational errors out of a beam plane. This, together with the treatments being delivered using multiple couch angles, may all contribute to the plan robustness. This effect is unlikely to be identified in studies relying on the static dose cloud approximation. It should be noted, however, that the MMWL phantom employed in this study only has 6 targets that are less dispersed along the anterior-posterior axis, which can also be another reason explaining the lack of correlation observed. The study could be benefited with the use of larger phantoms with more dispersed targets inside.

This study concluded a GTV-PTV margin of 0.5 mm was appropriate.
This value was generally larger than the theoretical margin calculated with the van Herk recipe [21] over a range of target-isocentre distances up to 8 cm (0.31 – 0.52 mm for 1-fraction patient and 0.33 – 0.40 mm for 3-fraction patients), but the smallest non-zero margin that the Elements TPS can grow in this case is 0.5 mm. Using this slightly larger margin provides some additional redundancy which could be an advantage as not all sources of geometrical uncertainty were measured in this study as they were considered beyond the scope of this project. Although not originally designed for SRS, the van Herk recipe [21] has been employed for margin derivation, with modifications made according to Tudor et al. (2020). This is an improvement over some other studies like Stanhope et al. (2020) which derived margins based on trigonometric relationships without considering the effect of random and systematic errors. Results showed 0.5 mm margins provided far better coverage than 0 mm margins, with 78% of all targets achieving the 98% coverage in the presence of 95th percentile errors, therefore coverage would be even better in typical scenarios. Although the application of this margin did increase the global normal brain dose, the local dose to normal brain, which is considered more important at this institution, increased only slightly and was still within constraints. Together, these results showed 0.5 mm PTV margins is effective in providing plan robustness to the extremes of geometrical uncertainties without severely affecting local normal brain doses.

The same set of shift values was applied to patients across all couch angles in this study, essentially removing any random error components in the process. In practice, the magnitude and direction of errors vary across different couch angles, further contributing to dose smearing. Despite this, findings from this study are consistent with a recent study by Eder et al. (2022) that recalculated doses to SMT SRS patient with the corresponding residual setup error at each individual couch angle [10]. The paper arrived at a similar conclusion of the lack of correlation of target dose coverage to either target-isocentre distance or target volumes. It also revealed the significance of imaging and applying couch corrections at each couch angle, which is the practice at our centre and may in part explain the small margin derived in this study in contrast with the 1 mm used in most centres across the country [11], although it is not reported how these centres derived their own margins. Using a 0.5 mm margin, instead of 1 mm, would lead to a significant improvement in the volume of normal brain tissue being spared. For example, the average radius of metastases being investigated in this study was approximately 5.6 mm, reducing the margin from 1 mm to 0.5 mm would mean a 21% reduction of normal brain tissue volume that overlapped the PTV.

5. Conclusion

In summary, the study had quantified the magnitude of geometrical uncertainties resulting from the residual patient setup errors and linac delivery errors, and proved the robustness of SMT-SRS plans under nominal scenarios despite no margins being applied, though the target coverage could still be compromised under near worst-case errors. In contrast with the assumptions made in several studies, there was limited correlation of target coverage with either target-isocentre distances or target volumes. It found a 0.5 mm margin would be appropriate, which is much smaller than the 1 mm margin used across many centres. Applying this margin can significantly improve the coverage relative to no margin and provide adequate levels of robustness to the measured errors, while maintaining a relatively low level of local normal brain dose. More work is needed to prove the effect of 0.5 mm margins on patients clinically.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References


