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RESEARCH PAPER

Impact of immobilisation and image guidance protocol on planning target volume margins for supine craniospinal irradiation

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ABSTRACT

Background: The setup errors during supine-CSI (sCSI) using single or dual immobilisation (SM, DM) subsets from two institutions were reviewed to determine if DM consistently decreased the required planning target volumes (PTV) margins and to identify the optimal image guidance environments.

Materials and methods: Ours and a sister institutional cohort, each with a subset of SM or DM sCSI and daily 3-dimensional online image verification sets, were reviewed for the cranial and spinal regions translational shifts. Using descriptive statistics, scatter plots and independent sample Mann-Whitney test we compared shifts in each direction for two subsets in each cohort deriving PTV margins (Van Herk: VH, Strooms: St recipes) for the cranial and spinal regions. Three image guidance (IG) protocols were simulated for two regions on the combined cohort with SM and DM subsets to identify the most optimal option with the smallest PTV margin. The IG protocols: 3F, 5F and 5FB where the systematic error correction was done using the average error from the first three, five and in the cranium alone (applied to both the cranium and spine, otherwise) for the first five set-ups, respectively.

Results: 6968 image sets for 179 patients showed DM could consistently reduce the PTV margin (VH/St) for the cranium from 6/5 to 4/3.5 (31.8/30.8%) and 6/4 to 4/3.5 mm (30.5/16.8%) for primary and validation cohort, respectively. Similarly, for the spine it was 10/8.5 to 6/5.5 (38.6/38.4%) and 9/7.7 to 7/6 (21.6/21.4%), respectively. The "5F-IG" resulted in the smallest margins for both the cranial (3 mm) and spinal region (5 mm) for DM with estimated 95% CTV coverage probability.

Conclusion: DM with 5F-IG would significantly reduce the required PTV margins for sCSI.

Key words: craniospinal irradiation; PTV margins; IGRT; immobilisation; motion

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Introduction

Craniospinal irradiation (CSI) is an integral component of curative treatment in several childhood brain tumours. However, CSI is known to be associated with various long-term toxicities, including cardio-pulmonary diseases and risk of second malignancies [1–3]. These are directly related to low dose spill which is typically associated with the 'exit dose' during photon-based CSI. Improved

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precision in the delivery of CSI can potentially reduce these long-term toxicities as well as improve survival outcomes [4, 5].

Precise delivery of CSI is challenging due to the complex shape and Magna size of the target volume leading to difficult immobilisation and daily reproducibility. This leads to increased random and systematic positioning errors. As a result, larger planning target volume (PTV) margins are required to account for setup uncertainty. The large PTV margins, in turn, increase the total irradiated volumes in these patients. With possible reductions in PTV margins, dosimetric as well long term clinical benefits can be achieved.

One of the methods to achieve reduction in the PTV margins can be to improve existing immobilisation and appropriate utilisation of image guidance tools in a routine clinical practice. Conventionally, head-neck thermoplastic immobilisation alone or with vacloc has been used during CSI and the PTV margins ranging from 3.8 to 11.5 mm have been recommended depending on the direction of displacement, margin recipe used, and anatomical region of verification (i.e. brain *vs.* upper spine *vs.* lower spine) [6–8]. In view of a very large and complex shape of target volume during CSI, the head neck thermoplastic alone may be inadequate for containing uncertainty and positioning error, especially of the lower spine. In our previous study we did not find the advantage of using vacuum immobilisation device over cranial thermoplast alone and, hence the practice of head neck thermoplast alone was continued [8]. Recently, we introduced an all in one base plate (low density AIO-2, Orfit®; Belgium) with dual immobilisation (DM) at head neck (four point) and pelvic (four point) thermoplastic (Orfit, Orfit®; Belgium) at our centre.

The use of daily image guidance and online correction may further considerably reduce setup uncertainty. However, daily image guidance in high throughput centres may have implications on optimal resource utilisation. Hence, a number of offline image verification and correction protocols have been developed and suggested in various other sites [9–11]. No action level (NAL) offline protocols are less labour-intensive than a shrinking action level protocol and are more widely adapted [12]. NAL protocols typically use the magnitude of motion or shifts from initial fractions of treatment delivery to derive an estimate of systematic error and correction is applied during subsequent treatment fractions. These image guided radiotherapy (IGRT) protocols have never been tested or reported in craniospinal irradiation. Overall, the adequate immobilisation and optimal image verification protocol could potentially reduce the random and systematic errors and, hence, allow for reduction of PTV margins.

In our institution (Tata Memorial Hospital; TMH), we recently adopted a DM using four-point head and neck and pelvic thermoplastics fixed on to an 'all in one' base plate for better immobilisation. All patients underwent supine CSI (sCSI) with daily image verification and online correction. With encouraging early trends in the shifts, this was implemented in our sister institution (Advanced Centre for Treatment, Research and Education in Cancer; ACTREC) as well. In this study, we review the findings in the two institutions as primary (TMH) and validation (ACTREC) cohort to see the impact of change in immobilization on PTV margins. Further, we test various IGRT protocols on the combined cohort to derive the optimal IGRT with the smallest PTV margin requirement.

Materials and methods

Data from consecutive patients treated with sCSI on multiple linear accelerator units from two institutions (2010–2019) with available daily 3-dimesional onboard image verifications sets for both cranial and spinal regions (≥ 80% times/fractions) were considered. The patients treated with sCSI on linac were planned on CT simulation images using departmental protocol as previously described elsewhere [13]. The patients from our institution (TMH) constituted the primary cohort while those from our sister institution (ACTREC) constituted the validation cohort.

Datasets formation

The use of DM with a universal baseplate instead of conventional single immobilization (SM) was initiated in the primary cohort in the year 2018. The SM includes using a low density head neck and shoulder high precision baseplate (Model 32110; Orfit®; Belgium) with low density head supports and a four-point thermoplastic orfit (Orfit®; Belgium) for head neck and shoulder immobilization. For DM, all in one low density baseplate (Model:

32301; Orfit®; Belgium) is used with low density head supports and two four-point thermoplastic orfits (Orfit®; Belgium); for head neck and shoulder, and abdomen-pelvis immobilization. All our therapists were already well trained with musing these baseplates and orfits for all sites, there was no learning curve or technical challenge expected. With encouraging feedback regarding easier setups and online matching, same was initiated later in 2019 at our sister institution forming the validation cohort in the study. For the purpose of this study, the patients treated using SM and DM in two cohorts formed two independent subsets in each cohort. To evaluate the impact of change in immobilization on motion and resultant PTV margins, the margins were evaluated separately for the two subsets in each cohort and were reviewed for consistency of impact in the two cohorts using one as the primary and the other as a validation cohort. To evaluate the impact of IGRT on PTV and select the optimal schedule, a combined cohort (primary and validation) for each subset type (single and dual subsets) were used.

Shifts/motion and PTV margin calculation

The translational motion, both at the cranial and the spine regions, recorded during the online correction using either cone-beam computed tomography (CBCT) or Megavoltage fan-beam computed tomography (MVCT), were reviewed and used. The co-registrations for the cranial region was verified at the skull base and for the spinal region at the lower spine-lumbar region registering bone with bone using rigid registration algorithms. The translational motion/shifts in vertical (antero-posterior), lateral and longitudinal (supero-inferior) directions were analysed, the rotational motion was not considered for the study.

The translational shift data for each direction were used to generate means and standard deviations, root mean squares of standard deviations and, subsequently, the random (σ) and systematic (Σ) errors for each cohort subset separately. The most commonly used margin recipes to derive PTV margins, namely Van Herks' (VH) and Strooms' (St) formulae [13], were used as below:

Van Herks' margin (VH)$= 2.5\,\Sigma + 0.7\,\sigma$
Strooms' margin (St) $= 2\,\Sigma + 0.7\,\sigma$

Using these formulae, margins required for each direction (vertical, lateral and longitudinal) for the cranial, and lower spine regions were derived. The mean of required margins in three directions at the cranium and spinal levels were estimated as the required PTV margins. These margins represent the expansions to account for both systematic and random errors without any image guidance protocol. The overall PTV margin requirement was estimated as the mean of PTV estimated in three translational directions.

Image guidance protocols

We simulated various no action level (NAL) offline correction environments on the online correction data set. These protocols are widely adaptable and clinically feasible especially in high volume centres. The following three hypotheses were tested:

3F: The magnitudes of motion during the first three treatment fractions (radiotherapy sessions) in each direction were averaged and deducted from motion in the rest of the treatment fractions. This is expected to reduce the systematic setup error partially. VH and St margins were calculated subsequently on the residual shifts during the rest of the treatment fractions.

5F: Similar to the 3F protocol, the average magnitude of motion during the first five treatment fractions is deducted from the rest of the fractions to generate VH and St margins on residual shifts.

5FB: Systematic error reduction done for the brain (cranial) region only by deducting five fraction-average motion of the cranial region from motion in the spine region. This hypothesis is based on a commonly prevalent concept among out therapists assuming that the reduction of systematic error in the brain (cranial) region could potentially reduce systematic error in the spine region as they may have a common source and one direction.

We compared the resultant PTV margins between these environments and arrived at an optimal protocol based on the least margins for both the cranium and spinal region for both single and dual subsets from an overall cohort of patients from both institutions. The overall PTV margin requirement was estimated as the mean of PTV estimated in three translational directions. To estimate the impact or contribution of IGRT in PTV reduction, the percentage change in PTV margin from no IGRT schedule was estimated for both the

Table 1. General patient characteristics

	Primary Cohort			Validation cohort		
	Single immobilization (n = 51)	Dual immobilization (n = 45)	Total (n = 96)	Single immobilization (n = 66)	Dual immobilization (n = 17)	Total (n = 83)
Age in years (median)	19	7	11	13	16	16
Gender						
Male	31	28	59	42	12	54
Female	20	17	37	24	5	29
Diagnosis						
Medulloblastoma	25	31	56	55	13	68
Others	26	14	40	11	4	15
Dose and fractionation (Median)	35 Gy/21 fractions	35 Gy/21 fractions	–	35 Gy/21 fractions	35 Gy/21 fractions	–
Treatment unit						
Tomotherapy	51	10	61	66	17	83
Other linear accelerator	0	35	35	–	–	–
Total image data sets						
Cranial	1004	812	1816	1286	415	1701
Spinal	993	800	1793	1280	378	1658
Median number of image sets per patient						
Cranial	21	21	21	21	21	21
Spinal	21	21	21	21	21	21

cranium and spine in the combined set from two institutions.

The immobilization set-up with image guidance protocol identified to be associated with the smallest PTV margins for cranium and spine were selected to see if calculated margins were able to cover > 95% times CTV in that cohort.

Statistical analysis

All the statistical analyses were done using the Statistical Package for Social Science software (IBM SPSS Statistics, SPSS. Inc v 23). The descriptive statistics were obtained as described above. The baseline characteristics within the cohorts and between cohorts were compared using the χ^2 test for statistical significance. The motion or shifts in various direction for various subsets were compared using the independent samples Mann-Whitney U test. The two institutional cohorts PTV margins were reviewed to see if the cranium and spine margins decreased consistently from using single to dual immobilization. The percent decline of the overall PTV margin with dual over SM subset in two cohorts was reviewed visually for consistency in the same direction and extent. Similarly, the percent decline in the overall PTV margin with an optimal IGRT schedule over none was estimated in two combined cohort's subsets (dual over single) to know the incremental benefit of IGRT.

Results

A total of 6968 image datasets from 179 patients from two cohorts were available. The detailed cohort and subset characteristics are shown in table 1. To note, the primary cohort dual immobilization subset had younger patients with a median age of 7 years treated on both kinds of machines (tomotherapy and conventional linear accelerators) than the SM subset with a median age of 19 years and treatment on tomotherapy alone. The validation cohort had a more similar age pattern in both subsets and was treated consistently on tomotherapy only. Overall, only 10% patients were treated under anaesthesia.

Shifts and margins

Primary cohort

In the primary cohort, the mean (standard deviation, SD) motion or shifts (mm) in the vertical,

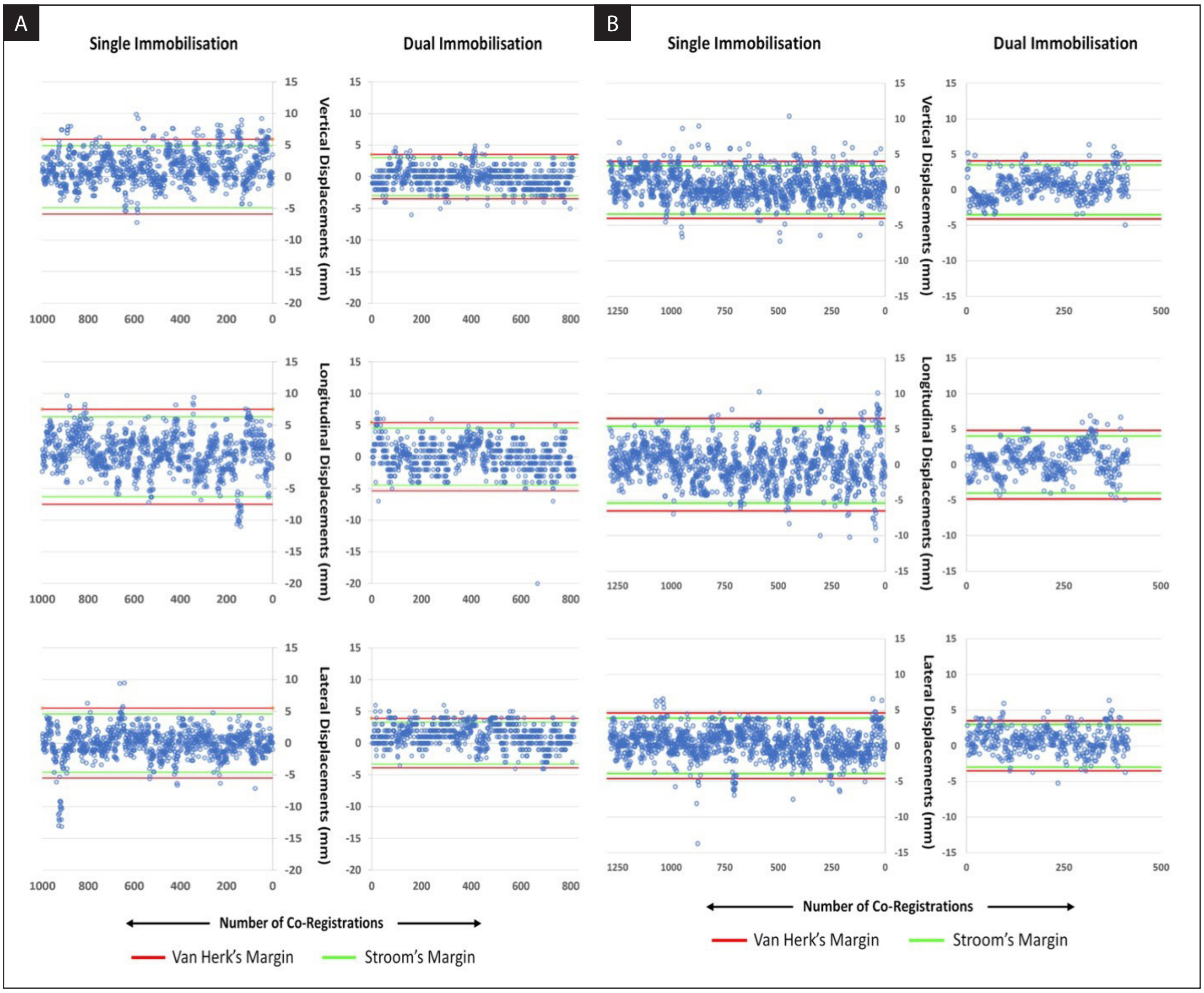

Figure 1. Scatter plots for Cranial region for motion in vertical, longitudinal and lateral directions comparing single and dual immobilisation in primary cohort (**A**) and validation cohort (**B**). Note the depiction of required isotropic Van Herk's and Stroom's margins without the use of image guidance protocol

longitudinal, lateral directions for the cranial region in patients with SM andDM were 2(3), 1(3), 0(2) and –0.2(0.2), 0.1(2.3), 1.3(1.7), respectively. Similarly, the spinal mean (SD) shifts in mm in vertical, longitudinal, lateral directions for SM and DM were –1(4), 1(5), 0(5) and 0.8(2.4), 0.2(2.8), –0.3(3.2) respectively. There was a statistically significant difference between vertical longitudinal and lateral shifts/motion between SM and DM for both the cranial ($p < 0.005$, each) and spinal regions ($p < 0.005$ each). The scatter plots for motion comparing two immobilisation sets are depicted in Figure 1A for the cranium and Figure 2A for the spinal region.

The margins calculated using VH for the cranium in the vertical, longitudinal and lateral directions with SM were 5.9, 7.5 and 5.5 mm which reduced to 3.5, 5.4 and 3.9 mm, respectively, with DM. The overall PTV margin for the cranium was reduced from 6.3 mm to 4.3 mm with DM (31.75% reduction). Similarly, using the St formulae, the vertical, longitudinal, lateral margins and overall mean PTV margin were reduced from 4.9, 6.3, 4.6 and 5.2 mm to 3.0, 4.5, 3.3 and 3.6 mm, respectively, with DM (30.77% reduction).

Again the VH margins for the spine in the vertical, longitudinal, lateral directions and overall mean PTV were reduced from 9.6, 10.5, 10.4 and 10.1 to 5.8, 6.2, 6.6 and 6.2 mm, respectively, with DM (38.61% reduction). The St margins for the spine in the vertical, longitudinal, lateral directions and overall mean PTV were reduced from 8.1, 8.8, 8.9 and 8.6 mm to 4.9, 5.3, 5.7 and 5.3 mm, respectively, with DM (38.37% reduction).

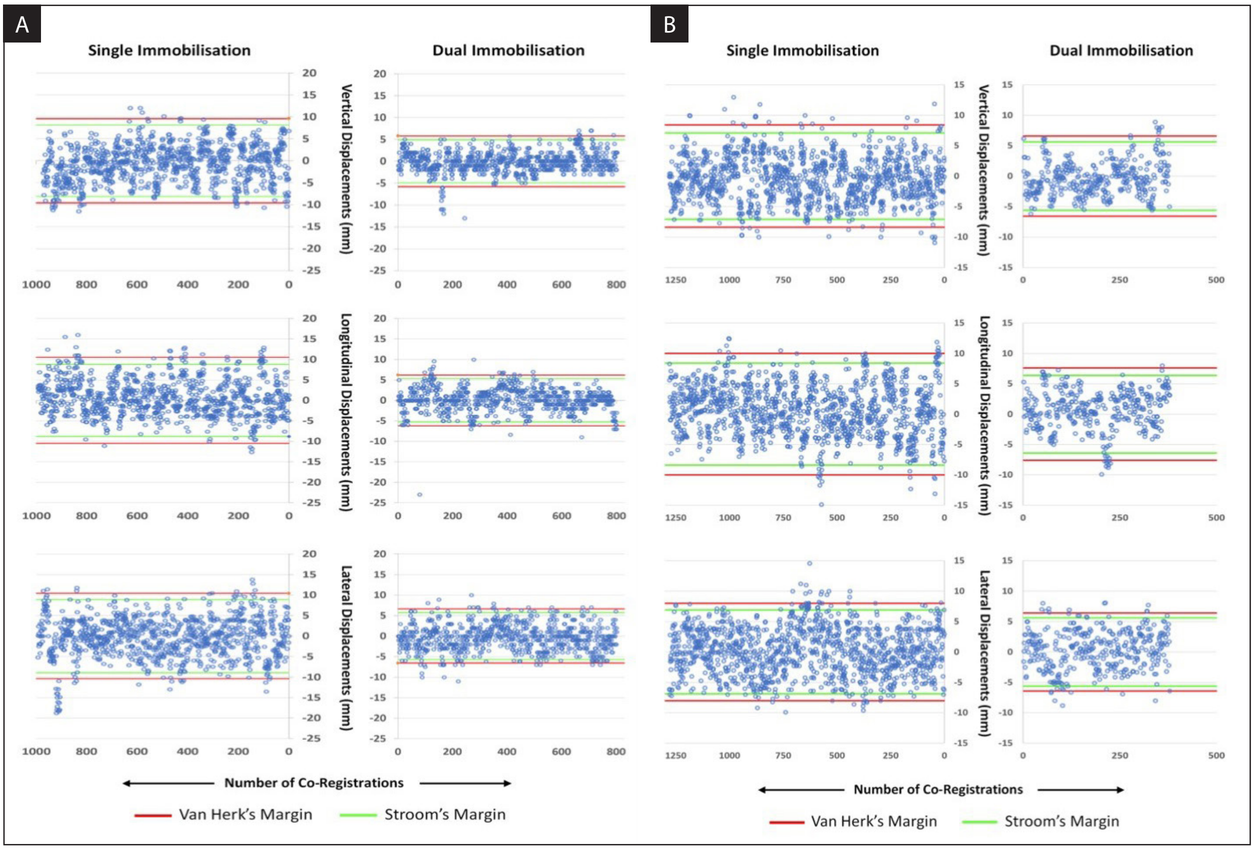

Figure 2. Scatter plots for Spinal region for motion in vertical, longitudinal and lateral directions comparing single and dual immobilisation in primary cohort (**A**) and Validation cohort (**B**). Note the depiction of required isotropic Van Herk's and Stroom's margins without the use of image guidance protocol

Validation cohort

The mean (standard deviation, SD) motion or shifts (mm) in the vertical, longitudinal, lateral directions for the cranial region in patients with SM and DM were 0.7(2), 0.2(2.8), 0.4(2) and 0.6(1.8), 0.7(2), 0.8(1.7), respectively. Similarly, the spinal mean (SD) shifts in mm in vertical, longitudinal, lateral directions for SM and DM were -0.4(3.7), 0.7(4.2), 0.2(3.8) and –0.3(2.8), 0.7(3.2), 0.4(3.2), respectively. The scatter plots for motion comparing two immobilisation sets are depicted in Figure 1B for the cranium and Figure 2B for the spinal region. The difference in distribution of shifts (motion) was not significantly different in the vertical direction for both the cranial and spinal regions ($p = 0.682$, 0.682, respectively), but significant in the longitudinal ($p = 0.002$, 0.002 respectively) and lateral directions ($p = 0.001$, 0.001, respectively) for both the cranium and spinal regions, respectively.

The VH margins for the cranium in the vertical, longitudinal, lateral directions and overall mean PTV were reduced from 4.0, 6.5, 4.6 and 5.9, to 4.1, 4.8, 3.5 and 4.1 mm, respectively with DM (30.51% reduction). With St formulae, the vertical, longitudinal, lateral margins and overall mean PTV margin were reduced from 3.4, 5.4, 3.9 and 4.2 mm to 3.5, 4, 3 and 3.5 mm, respectively, with DM (16.76% reduction).

Again, the VH margins for the spine in the vertical, longitudinal, lateral directions and overall mean PTV were reduced from 8.4, 10, 8 and 8.8 to 6.6, 7.6, 6.4 and 6.9 mm, respectively, with DM (21.59% reduction). The St margins for the spine in the vertical, longitudinal, lateral directions and overall mean PTV were reduced from 7.1, 8.4, 6.9 and 7.5 to 5.6, 6.4, 5.6 and 5.9 mm, respectively, with DM (21.33% reduction).

Overall, the DM could help consistently reduce the required PTV margin for both the cranium and spine in both cohorts. The decrease achieved was more for the spinal region than for the cranium, and more in the primary cohort than in the validation cohort (38–30% *vs.* 30–16 %).

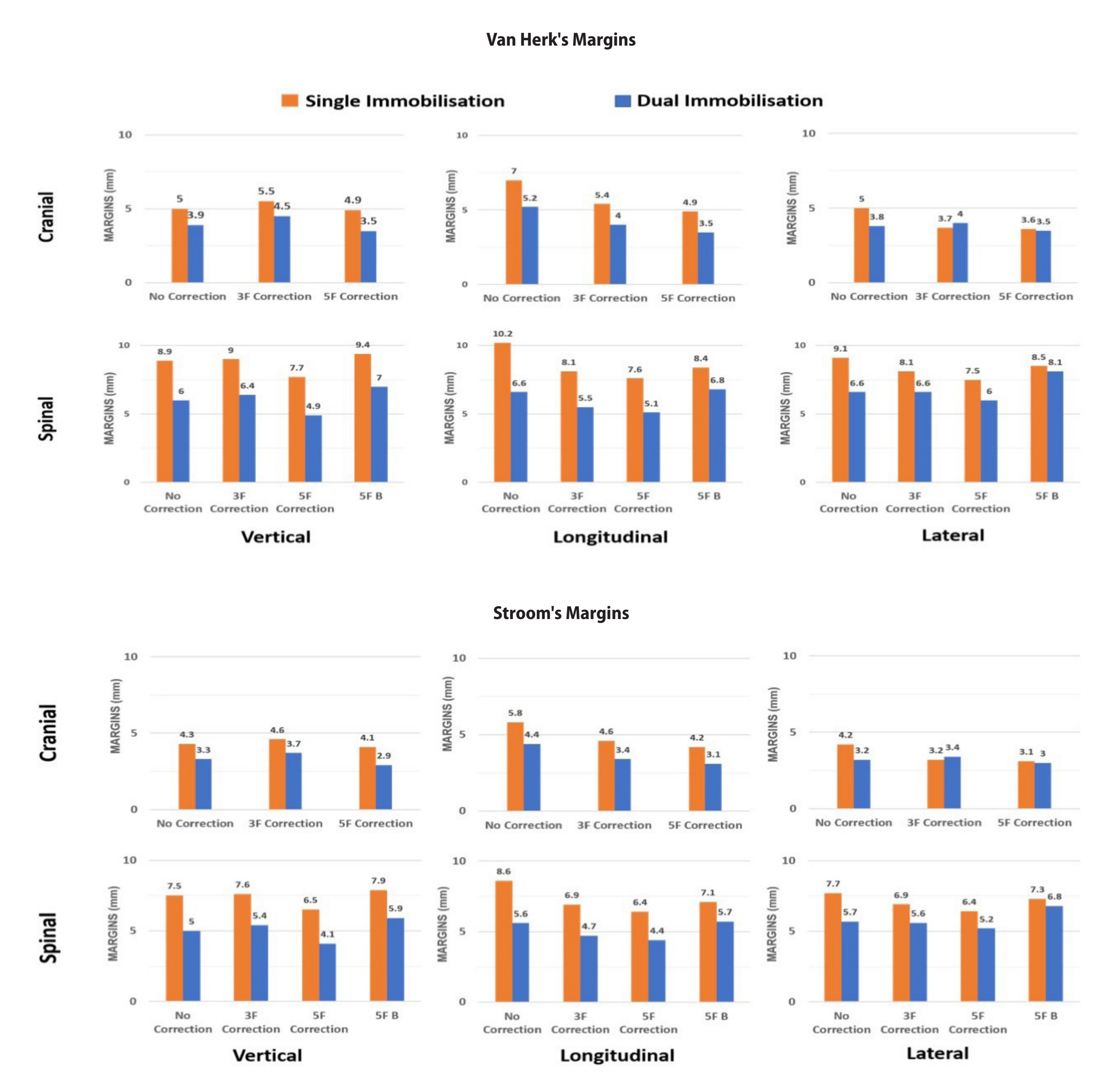

Figure 3. Van Herk's and Stroom's planning target volumes margins for cranial and spinal regions comparing single and dual immobilisation with various image guidance protocols

Optimal IGRT protocol

On testing various IGRT schedules on the combined cohort, the 5F-NAL protocol had the smallest magnitude of margins across all categories of motion, whereas, "No correction protocol" had the largest one, except for 5FB in the spinal region (Fig. 3). With 5F-NAL protocol implementation, the overall PTV margins (VH/St) for the cranium with SM and DM would be reduced from 5.7/4.8 to 4.5/3.8 mm and 4.3/3.8 to 3.5/3 mm, respectively. Similarly, for the spine, it would be reduced from 9.4/7.9 to 7.6/6.4 mm and 6.4/5.4 to 5.3/4.6 mm, respectively.

On rounding to PTV margins to the nearest full integer value, from SM with no IGRT to the combination of DM and 5F-NAL IGRT, a maximum reduction would be achieved for the cranium from 5 to 3 mm (40%) and for the spine from 9 to 5 mm (44.4%). This suggests about 10% further reduction in PTV margins can be achieved with a 5-NAL IGRT protocol over the choice of immobilisation. Also, testing for 95% CTV coverage for DM 5F-NAL IGRT combined cohort, the required PTV was estimated to be very similar to estimation from margin recipes (2.48 mm and 4.96 mm for the cranium and spinal region).

Discussion

Adequate immobilisation and the use of optimal image guidance is crucial for precise delivery of CSI and our study demonstrated that DM with image guidance using a 5F NAL protocol lead to maximum reduction in the required PTV margin. As per our knowledge, this is the largest study evaluating setup uncertainty during delivery of CSI. We investigated the influence of a type of immobilisation and impact of image guidance protocol on PTV margins.. We studied the setup motion in the cranial as well as spinal region with separate image verification sets taken during the same treatment setup and derived minimum isotropic margins required for cranial and the spinal PTV with SM and DM under various image guidance environments. Estimation of the thoracic spine PTV margins could have been beneficial for adult patients, but such images were not available consistently and, hence, were not perused.

Our study confirmed that better immobilisation leads to smaller translational errors and potential for reduction of PTV margins. All in one base plate with dual thermoplastics forms robust immobilisation with a total of 8 points of fixation on a single base plate and also has additional markers to aid alignment. This possibly contributed considerably to reducing random errors. In addition, image guidance using initial 5 treatment setups to a partially correct systematic error might have further contributed to reduced margins. Large data on inter-fractional motion with different immobilisation methods and various image guidance protocols may also guide individualization and tailoring of margins to optimize the strategy for image verification and margin derivation in sCSI.

A previous study by Al-Wassia et al. evaluated setup uncertainty in 27 patients who had undergone sCSI on helical tomotherapy [6]. Single set of images per patient were analysed and margins were calculated using various recipes. The study, however, does not evaluate margins required for different anatomical regions (cranial versus spine). They reported the mean displacements and added 2SD for their proposed margins which may not be the most appropriate way for deriving margins. The influence of various offline image verification methods or protocols was not studied either.

Implementing daily image verification in CSI can be challenging due to the need for multiple images per patient per fraction (at least two: cranium and spine). If intra-fraction motion is to be accounted for, further doubling of imaging would be needed. CSI delivery and set-up itself is cumbersome and needs long machine time, with increased number of imaging, verifications and set-ups it would further increase the on-machine time for patients. Considering CSI as mostly a treatment for young children, long time on a machine can be quite distressing and further increase the chances of intra-fraction motion. Multiple images per fraction would significantly increase the imaging dose per fraction. In the absence of any publication or recommendations supporting clinical benefit of daily imaging in CSI and considering logistic challenges it may pose in a high throughput centre such as ours, exploring suitable less than daily imaging protocol would be desirable. Identification of 3 mm for the cranium and 5 mm for the spine as a PTV margin with 5 F-NAL and DM seems quite practical and useful for centres like ours.

We have also previously reported the se-tup uncertainty in sCSI in the cranial upper spine and lower spine regions in 33 patients and demonstrated marginally higher magnitudes of margins compared to the current study [7]. In that study we did not find significant predictors for uncertainty in the subset analysis, either by age, need for anaesthesia or diagnosis. We, along with another study, demonstrated that there was a systematic increase in margins required from the brain towards the lower spine and advocating the need for differential margins for the brain and spine target volumes [7, 8].

Although, majority of the current study patients were treated on helical tomotherapy, 17 patients (24%) were treated on other conventional linear accelerators. Number of factors including age, shape and complexity of target volume, type of immobilisation, image verification protocol, etc. influence the setup uncertainty and, hence, the margins for PTV. These factors are well studied in various other disease sites such as head neck prostate cancers [15–17], but such data for sCSI are very limited. It may be very difficult to stratify for each and every variable with limited sample size, but, still, the current study presents a comprehensive evaluation of influence of immobilisation on setup uncertainty in sCSI along with defining an optimal offline image verification protocol.

Being a retrospective study, one of the limitations of our study is some heterogeneity in the population with higher median age in patients with SM and the influence of other factors related to treatment units. All patients with SMs were treated on Tomotherapy, which is a hindrance for rendering radiotherapy under anaesthesia due to long treatment duration and so is the availability of all fraction 3D image verifications. Since DM patients of all ages were treated on all treatment units with daily image verification, all age uniform data were available for comparison. This may have influenced the results at least in part. It should also be noted that in our previous study the age was not found to be a predictor for the translational motion in subgroup analysis [7]. We did not account for intra-fractional errors in this study which is another limitation of the study. Other limitations include non-availability of rotational errors data, PTV estimation for daily IGRT set-up and addressing challenges during actual online implementation of various motions at CSI subsites.

The study results potentially alter the practices in a sCSI delivery technique and, hence, improve precision. Reduction in PTV margins can potentially reduce irradiated volumes and low dose spills considerably and may translate to clinical benefit. The reduction in PTV margins can reduce toxicities associated with radiation therapy as has been shown in some other disease sub-sites [18, 19]. The standardization of IGRT protocol may reduce the chances of target miss during treatment with improving quality assurance of the whole process bettering outcome. Overall, this approach may lead to a gain in the overall therapeutic ratio in such patients.

Conclusion

Precise delivery of sCSI is challenging. Efficient immobilisation and optimal utilization of image verification protocols may significantly reduce set-up uncertainty and, hence, the magnitude of PTV margins. Success of new conformal radiation delivery techniques in the recent years and near future is heavily dependent on set-up accuracy and optimal image guidance. Accurate delivery of CSI may have clinically significant benefits in terms of improving target coverage and reducing acute and long-term toxicities associated with CSI leading to overall improvement of therapeutic ratio.

Conflict of interest

None declared.

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Part of the study was presented at the Congress of the International Pediatric Radiation Oncology Society (PROS) 2019 as a poster and was adjudged as the best poster. The current manuscript has included additional patients in the primary cohort and an additional validation cohort and is an Institutional ethic committee approved study.

Statistical analysis is done by Shivakumar Gudi and Arpana Siwach

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