

Scientific Article

Setup Accuracy in Craniospinal Irradiation: Implications for Planning Treatment Volume Margins



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Abstract

Purpose: Craniospinal irradiation (CSI) using tomotherapy has advantages over standard 3-dimensional techniques. However, there is a paucity of published data on craniospinal setup reproducibility to guide appropriate planning treatment volume (PTV) margins. We sought to evaluate the setup accuracy of patients undergoing CSI to optimize PTV margins.

Methods and Materials: We measured residual setup deviation between simulation computed tomography (CT) and daily megavoltage CT after couch shifts made by therapists after megavoltage CT-based image registration for 10 patients who completed CSI at our institution. Translational displacement values were recorded at the sella, top of T1, and top of L5 in the anteroposterior (AP) and lateral planes. Systematic and random error were calculated from displacement values. Using *z* score analysis, we calculated minimal PTV margins to encompass 90% of recorded fractions at each level. We evaluated whether patient characteristics predict for increased setup error using standard statistical techniques.

Results: The mean setup deviation in the AP plane across all treatments was 2.49, 3.40, and 3.83 mm at the sella, T1, and L5, respectively. Mean lateral setup error was 2.86, 4.02, and 5.46 mm at the sella, T1, and L5, respectively. Systematic error ranged from 0.75 to 1.01 mm at the sella, 1.09 to 1.37 mm at T1, and 1.30 to 1.50 mm at L5. Random error ranged from 1.35 to 1.41 mm at the sella, 1.48 to 1.73 mm at T1, and 2.26 to 2.37 mm at L5. The minimum margin to cover 90% of the treatments was 6.4, 8.2, and 10.5 mm at the sella, T1, and L5, respectively. There appeared to be a correlation between older age and lateral setup error in the L spine approaching statistical significance (*R*, 0.629; *P* = .052).

Conclusions: Setup error increases in the caudal direction of the spine and is greater in the lateral plane compared with the AP plane. We recommend a PTV margin of 5 to 7 mm in the brain and 10 mm in the spine.

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Introduction

Craniospinal irradiation (CSI) consists of radiation therapy delivered to the entirety of the craniospinal axis with the goal of eradicating tumor cells present in the cerebrospinal fluid. This treatment is most commonly

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offered to patients with hematologic malignancies and is the standard of care for treatment of pediatric medulloblastoma.^{1,2}

Radiation treatment to the craniospinal axis presents various challenges owing to the large, irregular treatment volume and close proximity to critical structures. Historically, CSI was delivered by 3-dimensional (3D) techniques, which necessitated junctioning of cranial and spinal treatment fields. Compared with 3D conformal CSI, helical tomotherapy improves dose conformity and normal tissue sparing.^{3,4} An added benefit of tomotherapy is treatment delivery in a single plan. Tomotherapy plans result in reduced radiation dose to nearby organs at risk compared with 3D plans, which is particularly important in patients with good prognosis.⁵ Setup reproducibility is critical to ensure coverage of the clinical target volume and avoidance of nearby organs at risk. The use of a daily megavoltage computed tomography (MVCT) has been shown to improve setup accuracy in patients undergoing tomotherapy for several types of cancers.⁶ However, image registration presents a challenge when treating a large field, and there remains the potential for setup error.

The clinical target volume (CTV) for CSI is comprised of the entirety of the brain and the subarachnoid space in the spine including nerve roots laterally.⁷ A planning target volume (PTV) margin is added to the CTV to account for setup variation. Smaller PTV margins result in dose reduction to nearby organs at risk; however, the PTV must be adequately large enough to account for setup error. The PTV margin should correct for both systematic error and random error to ensure target volume coverage. Systematic errors are deviations between the observed setup position and the expected or planned position. Systematic error is most commonly measured as the deviation between setup for a given fraction compared with the position at computed tomography (CT) simulation, which serves as the reference position. However, it is important to recognize that if CT simulation positioning is "incorrect," this will introduce a systematic error, as daily setup will deviate from the expected setup even if it

matches CT simulation setup. Random errors are interfraction setup errors. Systematic errors result in deviation in the same direction and similar magnitude for each fraction, whereas random errors vary in magnitude and direction for each fraction. Systematic errors will shift the cumulative dose distribution whereas random errors will blur the cumulative dose distribution. The European Society for Pediatric Oncology has published guidelines to assist in target volume delineation for intensity modulated radiation therapy-based CSI. These guidelines state that PTV margins should be based on departmental data. We sought to evaluate the setup accuracy of CSI patients treated at our institution to define PTV margins.

Methods and Materials

Patient characteristics

We retrospectively evaluated setup error for 10 randomly selected patients who underwent CSI by tomotherapy between May 2018 and January 2019 at our institution. Eight out of the 10 patients we evaluated were treated for hematologic malignancies (Table 1). The median age of patients treated was 46 years (range, 23-69). Median radiation dose was 23.4 Gy in 11 fractions (range, 18-36 Gy in 9-18 fractions).

Immobilization and computed tomography simulation

All patients underwent CT simulation extending from the top of the skull to the inferior aspect of the obturator foramen. All patients were simulated and treated in the supine position with arms placed over the chest. Vac-Lok, S frame, and an Aquaplast mask over the arms were used for immobilization. Before each treatment, an MVCT image was acquired and coregistered to

Table 1 Patient characteristics

Sex	Age	Diagnosis	Dose (Gy)	Number of fractions	PTV margin (mm)
M	23	Acute myeloid leukemia	18	9	10
F	60	Metastatic breast cancer	30	10	10
M	65	Diffuse large B cell lymphoma	36	18	12
M	54	Acute myeloid leukemia	18	10	10
M	31	Chronic myelogenous leukemia	24	12	10
M	38	Acute myeloid leukemia	24	16	8
F	30	Acute lymphoblastic leukemia	18	10	10
M	60	Mantle cell lymphoma	18	10	10
F	69	Mantle cell lymphoma	30	15	8
M	32	Medulloblastoma	23.4	13	6

Abbreviation: PTV = planning target volume.

kilovoltage CT images taken at the time of CT simulation. Radiation therapists aligned patients based on positioning at the level of the head, and then made manual adjustments to the treatment position based on setup differences from the MVCT to the kilovoltage CT. The registration was verified by a radiation oncologist at least once per week. All patients were treated on a helical tomotherapy machine using 6-MV photons. The helical tomotherapy couch allowed for patient positioning corrections in 3° of freedom (3-DoF), and gantry rotation allowed for positioning corrections in the roll axis.

Setup error calculations

We measured translational displacement values between simulation CT and daily MVCT after couch shifts made by therapists after MVCT-based image registration. The images used to measure translational displacements reflect patient setup after shifts were made by therapists just before start of radiation treatment. The first 10 radiation treatments were evaluated for each patient, with the exception of 2 patients who received only 9 treatments, yielding a total of 98 treatments evaluated. We measured displacement in both the lateral and anteroposterior (AP) planes at 3 predetermined locations: the sella, the superior aspect of T1, and the superior aspect of L5, yielding a total of 588 displacement values obtained. Maximum displacement was calculated based on hypotenuse values obtained from AP and lateral displacement values. AP and lateral displacement values were graphed as histograms for each craniospinal level (sella, T1, and L5) to evaluate the normality of the distribution for each data set. Pearson mode skewness was calculated for each data set, which is a measure of the symmetry of the data distribution and helps to identify outliers. The formulae used to calculate systematic and random error were based on methods described by Van Herk.⁸ Systematic error (Σ) was calculated as the quadratic sum of standard deviations of mean displacement values. Random error (σ) was calculated as the root mean square of the sum of standard deviations of mean displacement values.

We evaluated whether age, height, weight, or body mass index (BMI) predicted for increased setup error. Pearson correlation and analysis of variance were used for statistical analysis.

Safety margin calculation

To calculate the minimum safety margin necessary to cover the CTV for 90% of the patients with the 95% isodose line, we used the following equation described by Van Herk et al⁹: $PTV = 2.5(\Sigma) + 0.7(\sigma)$. For comparison, using Z-score analysis, we calculated the minimum PTV

margin required to encompass 90% of our recorded fractions at each anatomic level.

Results

Setup error by anatomic location

The mean setup displacement in the AP dimension across all treatments was 2.47 mm (Std Dev = 1.55), 3.40 mm (Std Dev = 1.86), and 3.82 mm (Std Dev = 2.20) at the level of the sella, T1, and L5, respectively. The mean displacement in the lateral plane was 2.86 mm (Std Dev = 1.46), 3.40 mm (Std Dev = 1.86), and 5.46 mm (Std Dev = 2.58) at the level of the sella, T1, and L5, respectively. The estimated mean maximum setup error in any direction was 4.01 mm, 5.51 mm, and 7.00 mm at the level of the sella, T1, and L5, respectively. Maximum setup error was the least at the level of the sella and the greatest at the level of L5 (Fig 1).

Systematic and random error

Systematic error (Σ) was lowest at the level of the sella (range, 0.75-1.01 mm) and highest at the level of L5 (range, 1.30-1.50 mm) (Fig 2). Random error (σ) was also lowest at the level of the sella (range, 1.35-1.41 mm) and highest at the level of L5 (range, 2.26-2.37 mm). Table 2 demonstrates the values obtained for mean translational displacement, systematic error, and random error in the AP and lateral dimensions by anatomic location.

Normality of data point distribution

Data for setup error at the level of the sella, T1, and L5 all demonstrated normal distribution. Average skewness among all data sets was 0.19 (range, -0.18 to 0.67). The data set with the greatest skewness was AP displacement at the level of the sella. All other data sets had a skewness less than 0.5.

PTV calculation

Applying Van Herk's formula, we calculated the margin necessary to cover the CTV for 90% of the patients with the 95% isodose line in both the AP and lateral dimensions. One millimeter of contour delineation variation was factored into this calculation; however, we did add additional margin for internal organ motion or intrafraction motion. Based on setup error in the AP dimension, we calculated PTV margins of 4.49 mm, 4.90 mm, and 4.84 mm at the level of the sella, T1, and L5,

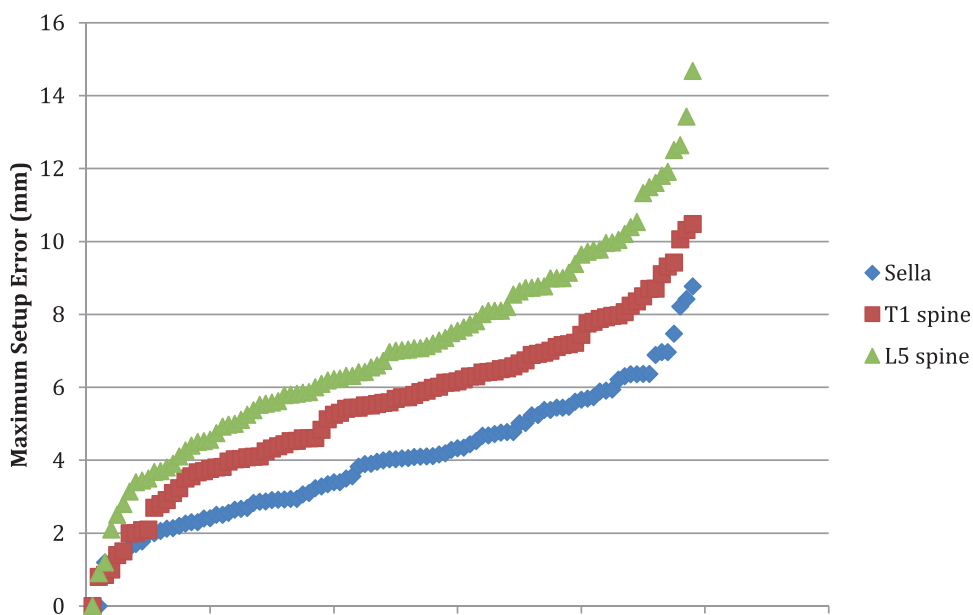


Fig. 1 Maximum displacement values by craniospinal level.

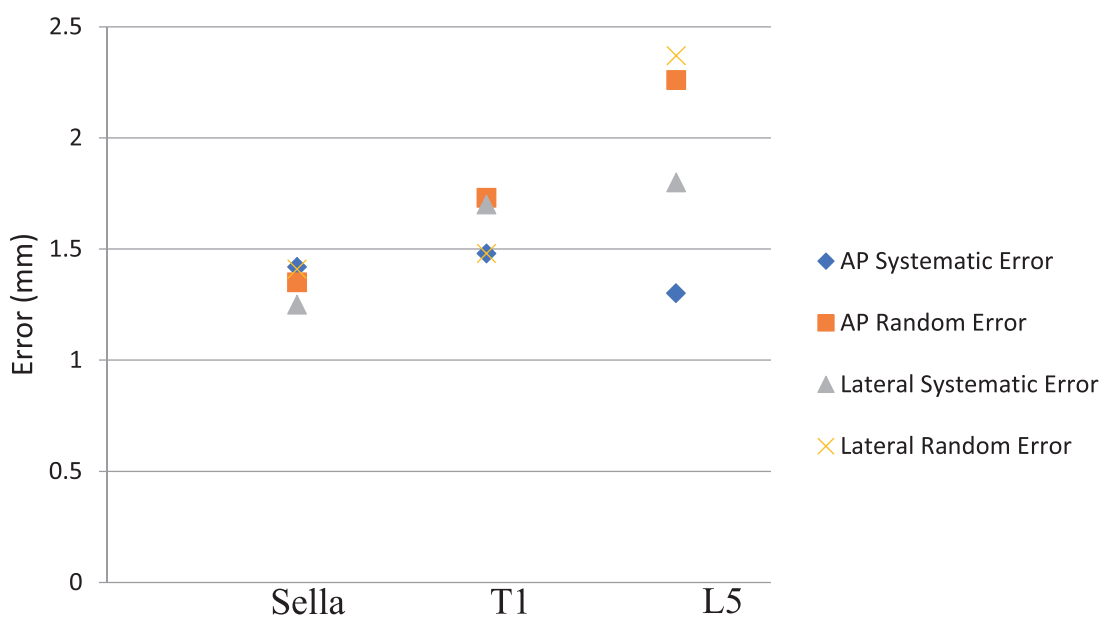


Fig. 2 Total random and systematic errors in the anteroposterior and lateral planes by anatomic level.

Table 2 Mean value, standard deviation, and random error by anatomic level

	AP plane			Lateral plane		
	M (mm)	Σ (mm)	σ (mm)	M (mm)	Σ (mm)	σ (mm)
Sella	2.49	1.01	1.35	2.85	0.75	1.41
T1	3.40	1.09	1.73	4.00	1.37	1.48
L5	3.82	1.30	2.26	5.43	1.50	2.37

Abbreviation: AP = anteroposterior.

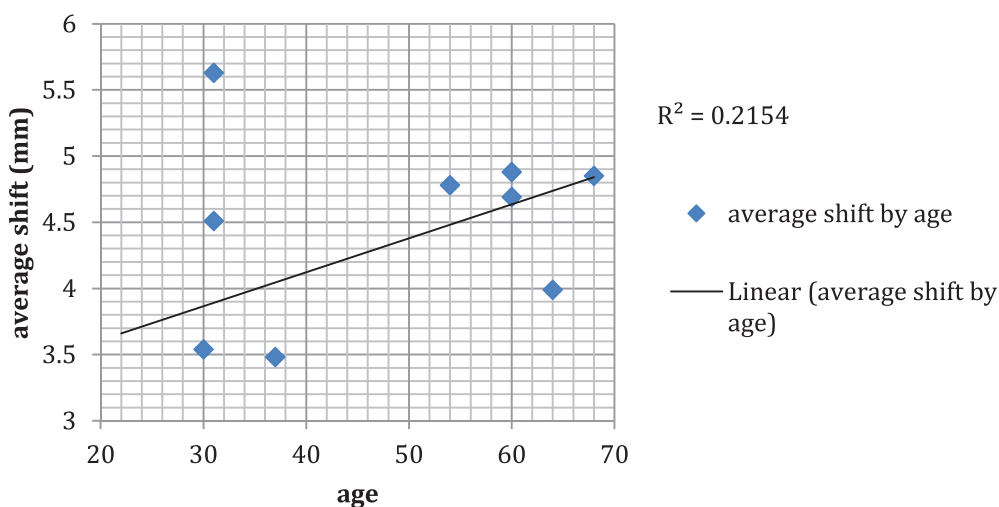


Fig. 3 Lateral setup error at the level of the L spine as a function of age.

respectively. Based on setup error in the lateral dimension, we calculated PTV margins of 4.11 mm, 5.28 mm, and 6.16 mm at the level of the sella, T1, and L5, respectively.

For the purposes of comparison, we calculated the minimum PTV margin to cover 90% of treatments in our cohort using Z-score analysis based on the estimated maximum translational displacement values. This method yielded a PTV margin of 6.4 mm, 8.2 mm, and 10.5 mm at the level of the sella, T1, and L5, respectively.

Patient characteristics and effect on setup error

Lateral setup error at the level of L5 correlated with older age, approaching statistical significance ($R, 0.629$; $P = .052$) (Fig 3). There was no significant correlation between height, weight, or BMI with setup error.

Discussion

Setup accuracy of tomotherapy for CSI was previously reported by Al-Wassia et al,¹⁰ who demonstrated systematic deviations in the range of 1.1 to 2.1 mm. Based on their findings, the authors recommended a uniform PTV margin of 3 mm. However, there have been additional studies to suggest that systematic setup error is not uniform throughout the craniospinal axis. Our results more closely align with those reported by Gupta et al,¹¹ in that setup error appears to increase from the brain to the lower spine. Another study reported that setup error is greater in the thorax and pelvis than in the brain, head, and neck.¹² The best explanation for these findings relates to

immobilization techniques. The S-frame fixes a patient's head, neck, and shoulders to the treatment couch, significantly limiting motion. However, the trunk is immobilized only by a Vac-Lok system, which allows for far greater mobility compared with the S-frame. An alternative explanation for this finding is that setup error will vary depending on the anatomic location at which radiation therapists are primarily positioning the patient. For example, if therapists position the patient at the level of the brain, we expect less setup deviation in the brain compared with the thorax or pelvis. Given that the patients included in our analysis were positioned by radiation therapists based on alignment at the level of the head, it is unsurprising that we found systematic and random error to be the lowest at the level of the sella.

Our results demonstrated that setup error was greater in the lateral plane compared with the AP plane. The PTV margins calculated using Van Herk's methodology reflected this, yielding larger lateral margins for the thoracic and lumbar spine compared with the AP margins. Decreased setup error in the AP plane can be explained by the fact that all patients were treated in the supine position on the treatment couch, thereby limiting motion in the posterior direction. Some may argue that an asymmetrical PTV margin (ie, a greater margin expansion laterally compared with in the AP dimension) would allow for further sparing of organs at risk. Rotational error in the lateral direction of even small magnitude becomes pronounced over a large treatment volume, and a limitation of tomotherapy is a 3-DoF couch that does not allow for changes in the roll, pitch, or yaw axes. Gantry rotation can correct for rotational deviation in the roll axis, but not pitch or yaw. A treatment couch allowing for setup verification in 6-DoF allows for correction of rotational errors in the roll, pitch, and yaw axes and could potentially allow for further decrease in the PTV margins.

CSI by tomotherapy results in treatment times of up to 30 minutes or more, in addition to the time necessary to acquire an MVCT and make manual shifts.¹³ A consequence of longer treatment times is higher probability for intrafraction setup error (ie, patient motion). Better immobilization techniques for the patient's trunk will likely reduce systematic setup error in the spine, and may therefore promote the use of smaller PTV margins in the spine. When calculating PTV margins using Van Herk's formula, we made the decision not to add any additional margin to account for intrafraction motion. One way to assess intrafraction motion in future studies would be to acquire an MVCT scan at the end of treatment and compare positioning to the pretreatment scan. We also did not add margin to account for internal organ motion because setup for CSI is guided by bony landmarks. In cases where a CTV includes or approaches organs with internal motion (eg, lungs, bladder, intestine), additional margin should be factored into the PTV margin calculation. A limitation of our study is that we followed our institution's practices regarding immobilization and setup verification methods; thus, we cannot guarantee that our findings are representative of CSI treatments at all institutions.

Previous reports have suggested that setup error increases with BMI.^{14,15} Our results did not support these findings; however, another limitation of our study is our small sample size. Seven out of 10 patients in our cohort had a BMI ≤ 23 , thus our cohort may have not been powered to identify correlations between BMI and setup error. We did identify a correlation between setup error and age approaching statistical significance, and adults in our cohort represented a wide distribution of ages (range, 23–69).

Comparing the PTV margins obtained using Van Herk's formula to those obtained from our Z-score analysis to cover 90% of treatments in our cohort, we found Van Herk's formula to yield smaller PTV margins. This was expected, as Van Herk's formula is designed to calculate the absolute minimum PTV margin based on interfraction variation. For example, if a patient consistently has a setup deviation of 10 mm across all treatments, the interfraction variation will remain small. Therefore, we recommend that the PTV margins obtained using Van Herk's formula should not be used as an absolute PTV margin, but rather as a cutoff for the minimum margin necessary to account for interfraction setup error. Our Z-score analysis yielded slightly larger PTV margins, which may be more practical. Thus, we recommend a PTV margin of 5 to 7 mm in the brain and 10 mm in the spine.

Absolute translational displacements will vary by patient and also by institution, as factors such as immobilization technique and PTV margin can affect systematic setup error. The patients in our cohort were treated with PTV margins ranging from 6 to 12 mm. Larger PTV margins may result in greater translational displacements

from CT sim to treatment position, because the CTV is more likely to be covered by the PTV regardless of small shifts.

Conclusions

Setup error in both the AP and lateral dimensions is the least in the sella and the greatest at L5. Therefore, setup error appears to increase in the caudal direction of the spine. Lateral setup error is greater than setup error in the AP plane.

Based on the values required to encompass 90% of this cohort's distribution, we recommend a PTV margin of 5 to 7 mm in the brain and 10 mm in the spine. Setup error may increase with age, though additional data may be necessary to reflect this correlation.

References

1. Pinnix CC, Yahalom J, Specht L, Dabaja BS. Radiation in central nervous system leukemia: Guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2018;102:53–58.
2. Martin AM, Raabe E, Eberhart C, Cohen KJ. Management of pediatric and adult patients with medulloblastoma. *Curr Treat Options Oncol*. 2014;15:581–594.
3. Parker W, Brodeur M, Roberge D, Freeman C. Standard and non-standard craniospinal radiotherapy using helical tomotherapy. *Int J Radiat Oncol Biol Phys*. 2010;77:926–931.
4. Sharma DS, Gupta T, Jalali R, Master Z, Phurailatpam RD, Sarin R. High-precision radiotherapy for craniospinal irradiation: Evaluation of three-dimensional conformal radiotherapy, intensity-modulated radiation therapy and helical Tomotherapy. *Br J Radiol*. 2009;82:1000–1009.
5. Parker W, Filion E, Roberge D, Freeman CR. Intensity-modulated radiotherapy for craniospinal irradiation: Target volume considerations, dose constraints, and competing risks. *Int J Radiat Oncol Biol Phys*. 2007;69:251–257.
6. Schubert LK, Westerly DC, Tomé WA, et al. A comprehensive assessment by tumor site of patient setup using daily MVCT imaging from more than 3,800 helical tomotherapy treatments. *Int J Radiat Oncol Biol Phys*. 2009;73:1260–1269.
7. Ajithkumar T, Horan G, Padovani L, et al. SIOPE – Brain tumor group consensus guideline on craniospinal target volume delineation for high-precision radiotherapy. *Radiother Oncol*. 2018;128:192–197.
8. Van Herk M. Errors and margins in radiotherapy. *Semin Radiat Oncol*. 2004;14:52–64.
9. Van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: Dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;47:1121–1135.
10. Al-Wassia R, Bahig H, Poon E, Parker W, Freeman C. Daily setup uncertainty analysis for craniospinal irradiation using helical tomotherapy. *Pract Radiat Oncol*. 2013;3:349–355.
11. Gupta T, Upasani M, Master Z, et al. Assessment of three-dimensional set-up errors using megavoltage computed tomography (MVCT) during image-guided intensity-modulated radiation therapy (IMRT) for craniospinal irradiation (CSI) on helical tomotherapy (HT). *Technol Cancer Res Treat*. 2014;14:29–36.

12. Karaca S, Başaran H, Koca T, Özbayrak F. An evaluation of inter-fractional set-up errors in patients treated with distinct immobilization equipment for varying anatomical regions. *Int J Med Physics, Clin Eng Radiat Oncol.* 2016;05:121–129.
13. Schiopu SR, Habl G, Häfner M, et al. Craniospinal irradiation using helical tomotherapy for central nervous system tumors. *J Radiat Res.* 2017;58:238–246.
14. Zhao J, Zhang M, Zhai F, Wang H, Li X. Setup errors in radiation therapy for thoracic tumor patients of different body mass index. *J Appl Clin Med Phys.* 2018;19:27–31.
15. Lin LL, Hertan L, Rengan R, Teo BKK. Effect of body mass index on magnitude of setup errors in patients treated with adjuvant radiotherapy for endometrial cancer with daily image guidance. *Int J Radiat Oncol Biol Phys.* 2012;83:670–675.