




Low-Dose Image-Guided Pediatric CNS Radiation Therapy: Final Analysis From a Prospective Low-Dose Cone-Beam CT Protocol From a Multinational Pediatrics Consortium

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Sara R. Alcorn, MD, MPH, PhD¹ , Xian Chiong Zhou, MS²,
Casey Bojecho, PhD³, Rodrigo A. Rubo, BS⁴, Michael J. Chen, MD⁵,
Karin Dieckmann, MD⁶, Ralph P. Ermoian, MD³, Eric C. Ford, PhD³,
Daria Kobyzeva, MD⁷, Shannon M. MacDonald, MD⁸, Todd R. McNutt, PhD¹,
Alexey Nechesnyuk, MD⁷, Kristina Nilsson, MD, PhD⁹, Hakan Sjostrand, BS⁹,
Koren S. Smith, MS¹, Markus Stock, PhD⁶, Erik J. Tryggestad, PhD¹⁰,
Rosangela C. Villar, MD⁴, Brian A. Winey, PhD⁸, and Stephanie A. Terezakis, MD¹¹ 

Abstract

Background: Lower-dose cone-beam computed tomography protocols for image-guided radiotherapy may permit target localization while minimizing radiation exposure. We prospectively evaluated a lower-dose cone-beam protocol for central nervous system image-guided radiotherapy across a multinational pediatrics consortium. **Methods:** Seven institutions prospectively employed a lower-dose cone-beam computed tomography central nervous system protocol (weighted average dose 0.7 mGy) for patients ≤ 21 years. Treatment table shifts between setup with surface lasers versus cone-beam computed tomography were used to approximate setup accuracy, and vector magnitudes for these shifts were calculated. Setup group mean, interpatient, interinstitution, and random error were estimated, and clinical factors were compared by mixed linear modeling. **Results:** Among 96 patients, with 2179 pretreatment cone-beam computed tomography acquisitions, median age was 9 years (1-20). Setup parameters were 3.13, 3.02, 1.64, and 1.48 mm for vector magnitude group mean, interpatient, interinstitution, and random error, respectively. On multivariable analysis, there were no significant differences in mean vector magnitude by age, gender, performance status, target location, extent of resection, chemotherapy, or steroid or anesthesia use. Providers rated >99% of images as adequate or better for target localization. **Conclusions:** A lower-dose cone-beam computed tomography protocol demonstrated table shift vector magnitude that approximate clinical target volume/planning target volume expansions used in central nervous system radiotherapy. There were no significant clinical predictors of setup accuracy identified, supporting use of this lower-dose cone-beam computed tomography protocol across a diverse pediatric population with brain tumors.

¹ The Johns Hopkins Hospital, Baltimore, MD, USA

² The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

³ University of Washington, Seattle, WA, USA

⁴ Centro Infantil Boldrini, São Paulo e Região, Brazil

⁵ Grupo de Apoio ao Adolescente e à Criança com Câncer, São Paulo, Brazil

⁶ Universität Klinik Für Strahlentherapie und Strahlenbiologie, Vienna, Austria

⁷ Federal Scientific Clinical Center of Children's Hematology, Oncology and Immunology, Moscow, Russia

⁸ Massachusetts General Hospital, Boston, MA, USA

⁹ Uppsala University Hospital, Uppsala, Sweden

¹⁰ Mayo Clinic, Rochester, MN, USA

¹¹ Department of Radiation Oncology and Molecular Radiation Sciences, University of Minnesota, Minneapolis, MN, USA

Corresponding Author:

Stephanie A. Terezakis, Department of Radiation Oncology and Molecular Radiation Sciences, University of Minnesota, 420 Delaware St., Minneapolis, MN 55455, USA.

Email: sterezak@umn.edu



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Keywords

radiotherapy, image-guided, IGRT, brain neoplasms, prospective study

Abbreviations

CBCT, cone-beam computed therapy; CI, confidence interval; CNS, central nervous system; CT, computed tomography; CTV, clinical target volume; IGRT, image-guided radiotherapy; KPS, Karnofsky Performance Status; LA, laser alignment; LD-CBCT, low-dose cone-beam computed therapy; LME, linear-mixed effect; pCT, planning computed tomography; PTV, planning target volume; SD, standard deviation; VM, vector magnitude; XVI, X-ray volume imaging; QA, quality assurance; 3D, 3-dimensional.

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Background

Image-guided radiotherapy (IGRT) has become standard practice in treatment of the central nervous system (CNS) in pediatrics.¹ Through the convergence of advances in medical imaging and increasingly conformal radiotherapy techniques, IGRT has been successfully employed to improve treatment accuracy and precision while allowing for shrinkage of treatment margins and dose-escalation approaches.²⁻⁶

The most commonly employed form of IGRT used in the treatment of pediatric CNS targets is cone-beam computed tomography (CBCT), generally performed daily prior to delivery of radiation. As compared to pretreatment 2-dimensional imaging such as portal and kV planar X-ray techniques, CBCT provides 3-dimensional (3D) imaging with improved soft-tissue delineation at reasonably low radiation doses.^{7,8}

The benefits of CBCT in children must be weighed against notable risks. Although individual CBCT scans can be completed in approximately 2 minutes, the additive excess time attributable to CBCT over the course of many patients can be substantial. Monetary costs associated with CBCT vary by institution but can also be significant and prohibitive. Most importantly, although CBCT is associated with relatively low radiation dose as compared to diagnostic computed tomography (CT), individual scans using standard imaging protocols may still contribute up to approximately 30 mGy per scan^{9,10} and lead to substantive radiation dose over the course of several weeks of treatment. Dose attributable to IGRT is particularly important to consider in pediatrics due to concern for late effects related to both cumulative radiation exposure and distribution of radiation dose.¹¹⁻¹³ For example, Ding and Coffey estimated the dose to normal tissues delivered by a standard CBCT protocol (125 kVp, 80 mA, 25 ms) and found that the dose was greatly dependent on patient size, with higher doses delivered to normal structures in pediatrics versus adults. Tissues with a larger atomic number were found to receive higher dose, largely attributable to the photoelectric effect at the kV range for these materials. Consequently, dose to bone was found to be 2 to 4 times higher than that to soft tissues, with an estimated 4500 to 8400 mGy to bone over 25 to 35 fraction course from CBCT.¹⁴ This may have particular significance for treatment of pediatrics, where dose to bone may impair bone growth.

Despite these concerns, clinical predictors of setup accuracy within the pediatric population for low-dose CBCT

(LD-CBCT) for IGRT are not well-defined. Yet, low-dose CBCT protocols may allow for adequate target localization while minimizing radiation exposure and subsequent risk of late toxicity. Thus, we describe a standardized LD-CBCT protocol for CNS IGRT that was prospectively employed across an international pediatrics consortium. Specifically, we analyze parameters of setup error, assess for clinical predictors of setup accuracy, and report physician satisfaction with target localization using the LD-CBCT protocol.

Methods

Study Design

Providers from 7 international institutions with dedicated pediatrics expertise participated in prospective data collection for CNS IGRT practices in patients ≤ 21 years, between September 2010 to August 2015. A LD-CBCT protocol was prospectively defined by the physicists and physicians from the member institutions of the consortium. The imaging system used included an X-ray volume imaging (XVI) system, an onboard kV CBCT, and a planar imaging system (Elekta, Inc, Stockholm, Sweden). The protocol employed across institutions used a partial scan, S10 collimator, no filter (or F0 filter without a bow-tie component), 183 frames (approximate), 100 kVp, and 31.5 mAs. The imaging systems in this study conform to the standards and values listed in the AAPM Medical Physics Practice Guideline #2a on quality assurance (QA) of IGRT systems.

Radiation Dose From CBCT

The methodology utilized for dose measurements followed that described in the work of Siewerdsen et al.¹⁵ This method applied the recommendations of TG 111 for¹⁶ cone-beam scans and utilized a thimble ion chamber (0.6 cm³ Farmer chamber) for point-dose measurements in a standard computed tomography dose index (CTDI) phantom. Here, we utilized the smaller 16 cm diameter “head” CTDI phantom (which is more akin to pediatric sizes and provides a more conservative measure of dose than the alternative 32 cm diameter phantom size). Measurements were made at the center of the phantom and at 4 cardinal (peripheral) positions, which were weighted into a single value as follows:

$$D_w = \frac{1}{3}D_c + \frac{2}{3}\bar{D}_p$$

where D_c is the central measured dose, \bar{D}_p is the average of peripheral doses, and D_w is the weighted average reported in units of mGy. As described by Siewerdsen et al., the metric D_w is analogous to the standardized metric $CTDI_w$ utilized for multi-detector row computed tomography (MDCT) applications.¹⁵ An important difference is that the $CTDI_w$ conventionally utilizes a 100-mm pencil chamber, which, as described in TG 111, has conceptual inadequacies for its application to wide beam geometries such as CBCT.¹⁶

Study Population

All pediatric patients treated with conventionally fractionated photon IGRT with CBCT to CNS sites during the study period were included. Due to differences in QA protocols, patients undergoing hypofractionated stereotactic radiotherapy were excluded from this analysis. Because excessive setup variability may be expected on the first imaging session, data from imaging day 1 were not included in the analysis. This study was approved by the institutional review board (NA_00083758) at the Johns Hopkins University School of Medicine and at the participating institutions.

Radiation Planning and Patient Setup

All patients underwent planning CT (pCT), and staff radiation oncologists delineated gross target volume and applied a clinical target volume (CTV) and institution-specific planning target volume (PTV) expansions to each plan. Planning target volume expansions ranged from 3 to 5 mm. Prior to treatment, patients were immobilized with the same techniques used at the time of the pCT. Laser alignment (LA) to surface marks was performed, followed by CNS-directed CBCT scans. Cone-beam computed tomography images were registered to bone on the pCT. Automatic registration was used for 3D image registration, comparing the initial CBCT with the reference pCT. The software (XVI, Elekta, Inc, Stockholm, Sweden) supports 3 methodologies for the alignment, labeled as “seed, bone, grey value.” Bony alignment was used here. For this method, the software employed a chamfer edge matching algorithm.¹⁷ The 3D region of interest for this registration was restricted to a “clipbox,” which was manually adjusted to include the relevant visible bony anatomy for each patient.¹⁸ The relevant areas of interest would be expected to vary by clinical scenario and were determined at the treating physicians’ discretion.

Differences in positional setup with LA versus CBCT were calculated in the x (transverse), y (superior–inferior), and z (anterior–posterior) translational directions, and the treatment table was shifted accordingly to overlap the pCT and CBCT image sets. Initial alignment to laser, CBCT acquisitions, and physical table shifts were performed by radiation therapists specifically trained in CBCT technology. Prior to or following

each treatment, a radiation oncologist reviewed XVI from CBCT to confirm setup.

Analysis of Setup Difference Between LA and CBCT

The difference in setup with LA alone versus with CBCT was represented by the values of the physical table shifts in the x , y , and z translational directions. These data (measured in millimeters) were entered into MOSAIQ Oncology Information System (Elekta, Inc).

Potential Predictors of Setup Accuracy

Variables considered to be potential predictors of setup accuracy were selected by consensus agreement of providers from participating institutions prior to initiating the protocol. Age, baseline Karnofsky Performance Status (KPS), gender, IGRT target location, immobilization device used, extent of resection, chemotherapy use, baseline steroid use at time of IGRT initiation, and anesthesia use during treatment were assessed as potential predictors of setup accuracy. Age was defined in years at the time of initiation of radiotherapy. Baseline KPS was rated by treating physicians on a scale from 0 to 100 in units of 10 at the time of initiation of IGRT. The location of the target for IGRT was designated as originating in the supratentorial versus infratentorial fossa by the treating physician. Targets requiring craniospinal or whole ventricular radiation were not included while analyzing for predictors of setup accuracy. Immobilization type was documented as a short versus long thermoplastic mask, with short masks reaching the chin and long masks extending to immobilize the shoulders. For patients undergoing resection, the treating physician classified the extent of resection as consistent with gross residual versus no gross residual disease based on the reports of postsurgical diagnostic imaging. For patients receiving chemotherapy, this variable was classified as being delivered prior and/or concurrent to IGRT. Baseline steroid use and anesthesia use during IGRT were recorded as dichotomous variables.

Outcome Measures

In order to evaluate the LD-CBCT protocol, we assessed setup accuracy as a function of both (1) relatively objective measures of positioning uncertainty and (2) subjective physician ratings of image quality.

Setup positioning uncertainty. As a proxy for setup accuracy with the LD-CBCT protocol, we analyzed positioning error using table shifts from setup to surface marks with LA versus CBCT. Per the literature, positional error is considered to be comprised of both systematic (interpatient) and random (inter- and intrafraction) components.¹⁹ Table shifts between expected position as delineated by surface marks and actual position at the time of CBCT permitted measurement of interpatient systematic and inpatient random error. Similar methodology for capturing positioning error using table shifts has been described.¹⁸ Although establishing efficacy of the LD-CBCT protocol

would ideally involve direct comparison of positioning error from protocol images to those rendered from standard dose CBCT for each patient, the excess radiation exposure would be prohibitive of such a direct analysis in the pediatrics population. As such, this study assumes that LD-CBCT could be considered sufficient for use in setup if table shifts from LA versus LD-CBCT are similar in magnitude to those measured from LA versus standard dose CBCT.

The vector magnitude (VM) of the table shifts was calculated, providing a 3D expression of table shifts following LD-CBCT. Vector magnitude was defined as:

$$\text{Vector magnitude} = \sqrt{(x^2 + y^2 + z^2)},$$

where x = table shift in the transverse direction, y = table shift in the superior–inferior direction, and z = table shift in the anterior–posterior direction. The table shifts in the x , y , and z direction as well as the VM were each analyzed as a dependent variable using a linear mixed-effect (LME) model.

Of note, routine repeat CBCT was not performed after treatment. As such, there was no estimation of the intrafraction uncertainty.¹⁹

Physician ratings of image quality. The treating physicians rated a subset of CBCT for image quality relative to target localization. Ratings were performed on a Likert scale with values of excellent, adequate, inadequate, or poor for target localization, based upon their ability to render a clinical judgment using the imaging to assess anatomic alignment. An “adequate” image contained the minimum sufficient quality and information needed to render a clinical decision, whereas an “excellent” image surpassed these minimum requirements, thus permitting ease of decision-making. An “inadequate” CBCT—while perhaps not poor in quality—did not contain adequate information to readily render a clinical decision. A “poor” CBCT was inadequate in image quality and did not provide sufficient information for the clinical decision.

Data Analysis

Descriptive statistics were used to characterize patient and treatment features including mean age, median KPS and radiation dose, and frequency of categories for gender, race, immobilization device used, steroids and anesthesia requirements, and surgical and chemotherapy interventions used.

Parameters of positioning uncertainty were analyzed using mixed linear models. These models were clustered by patient and institution to account for the effects of repeated measures within the same patient and potential variations between treating institutions, respectively. Random effects for patients and institutions were assumed; no other random or fixed effects were considered. Estimates in the x , y , and z translational directions were determined using normal mixed-effect models; VMs were estimated using log-normal mixed-effect models. In these models, group mean error for each translation direction or VM was estimated as the mean (across patients) of the mean shift value for each patient over all fractions. Total variance was set

equal to the sum of between-patient, between-institution, and within patient variances. Systematic interpatient and inter-institution errors were estimated by the square roots of the between-patient and between-institution model covariances, respectively. Measurable random error was estimated as the square root of model residuals, representing (within patient) interfraction uncertainty.

Potential predictors of positioning uncertainty were evaluated for the VM group mean error using a univariate log-normal mixed model, again clustered by patient and institution. Fixed effects were assumed for the potential predictor variables.

Correlation between cranial volume and patient age was tested using Spearman ρ . P value for significance was $<.05$. Additional statistical details of the above models are listed in Supplementary Material. All analyses were performed using SAS 9.4 (SAS Institute, North Carolina) and R 3.2.2.

Results

The IGRT characteristics for 2179 pretreatment CBCT scans from 96 patients were collected and used to estimate setup accuracy parameters. Demographic data were available for 86 patients and were used to assess for predictors of setup accuracy. Primary histologies were 47% glioma, 12% medulloblastoma, 11% ependymoma, 5% craniopharyngioma, and 25% other (including primitive neuroectodermal tumor, germinoma, Langerhans cell histiocytosis, atypical teratoid rhabdoid tumor, epidermoid tumor, and pineal parenchymal tumor). Table 1 describes patient and treatment characteristics.

Radiation Dose From CBCT

Peripheral doses measured ranged from 0.4 to 1 mGy, and the central dose was measured to be 0.8 mGy. The weighted average, D_w , was calculated to be 0.7 mGy. The spread of doses was consistent with that of a partial scan (see Discussion section). It should be noted as well that the peripheral dose was not uniform because a partial scan was utilized (ie, 180° plus fan), leading to the range of peripheral doses measured (0.4–1 mGy), in which the lowest dose correlates to the surface of the phantom where the X-ray beam is nonincident.

Parameters of Positioning Uncertainty

Group mean error in the translational directions estimated from the LME model was 0.21 mm (95% confidence interval [CI]: -0.15 to 0.58 mm) for transverse, 0.21 mm (95% CI: -0.41 to 0.83 mm) for superior–inferior, and -0.49 (95% CI: -1.21 to 0.23 mm) for anterior–posterior orientations. The VM group mean error was 3.13 mm (95% CI: 2.53–3.87). Interpatient error ranged from 1.32 to 1.63 mm in the translational directions and was greater than interinstitution error (range 0–0.45 mm). The VM interpatient error was also greater than VM interinstitution error at 3.02 and 1.64 mm, respectively. Interpatient error and interinstitution error accounted for 65% and 19% of variability in the model, respectively. Random error

Table 1. Patient and Treatment Characteristics.

Patient and Target Characteristics (n = 86)	
Age in years—median (range) ^a	9 (1-20)
Gender, male—n (%) ^b	32 (56%)
Race—n (%) ^c	
White	36 (61%)
Black	10 (17%)
Other	13 (22%)
KPS—median (range) ^d	80 (40-100)
Tumor location—n (%) ^e	
Supratentorial	30 (43%)
Infratentorial	19 (27%)
Other	21 (30%)
IGRT characteristics ^f	
Total dose—median (range) ^g	54 Gy (24-59.4 Gy)
Immobilization device—n (%) ^h	
Short mask	43 (68%)
Long mask	20 (32%)
Baseline steroids use—n (%) ⁱ	
Yes	38 (48%)
No	41 (52%)
Anesthesia required—n (%) ^j	
Yes	26 (32%)
No	55 (68%)
Other treatment characteristics	
Surgical resection—n (%) ^k	
Yes	54 (68%)
No	26 (32%)
Extent of resection—n (%) ^l	
Gross residual disease	17 (40%)
No gross residual disease	25 (60%)
Chemotherapy—n (%) ^m	
Pre- or concurrent with IGRT	41 (68%)
After IGRT	15 (25%)
None	5 (8%)

Abbreviations: KPS, Karnofsky Performance Status; IGRT, image-guided radiotherapy.

^aMissing data: 2. ^bMissing data: 29. ^cMissing data: 27. ^dMissing data: 5. ^eMissing data: 16. ^fMissing data: 6. ^gMissing data: 23. ^hMissing data: 7. ⁱMissing data: 5. ^jMissing data: 6. ^kMissing data: 23. ^lMissing data: 27. ^mIncludes sites requiring craniospinal and whole ventricle radiation.

ranged from 1.60 to 1.69 mm in the translational directions, with VM of 1.48 mm. Random error accounted for 16% of variability in the model (see Figure 1).

Potential Predictors of Positioning Uncertainty

Table 2 shows the results of the univariate model for predictors of positioning uncertainty as estimated by VM. Accounting for repeated measures between individuals as well as the potential effect of different institutions, there were no statistically significant differences between VM based on age, gender, baseline KPS, target location, extent of resection, chemotherapy timing, baseline steroid use, or anesthesia requirement (all *P* values > .05). Immobilization device was not shown in the result because the model did not converge when this variable was included.

Post Hoc Analysis of Cranial Volume

A total of 24 patients were evaluated for cranial volume at the Johns Hopkins University School of Medicine site. Mean age for this subgroup was 11.1 (SD 5.9, range 3-20 years), which is similar to that of the full cohort. Mean cranial volume was 12128.8 cm³ (standard deviation [SD]: 1672.4). There was no significant correlation between age and cranial volume (Spearman $\rho = 0.095$, *P* = .660). Given no significant correlation between cranial volume and age, the cranial volume variable was not selected for inclusion into statistical models.

Physician Rating of Image Quality

Likert scale ratings by physicians for image quality were recorded for 173 LD-CBCT scans. All images were acquired using the same CBCT protocol as defined in the study. Only 1 scan was rated as inadequate, with the remainder of the scans categorized as adequate or excellent for target localization (see Figure 2). Cone-beam computed tomography was repeated at a higher dose for the 1 scan that was rated as inadequate. Given that authors could not conclude if there was a meaningful clinical difference between “excellent” and “adequate” image quality in this patient population, no statistical comparisons were made on the basis of ratings of image quality.

Discussion

In the present study, an LD-CBCT protocol was prospectively defined and employed for CNS radiotherapy across a consortium of 7 international institutions with pediatrics expertise. Additionally, we were able to prospectively collect measures of setup positioning uncertainty in this vulnerable population. To our knowledge, this is the first international study of its size to evaluate the feasibility of an LD-CBCT protocol in pediatrics. Additionally, it is the first to estimate parameters and assess predictors of setup accuracy with LD-CBCT for this population.

Regarding the dose from CBCT in this study, we determined that our protocol indeed fell within a lower-dose range. In a comparison study of XVI and onboard imaging CBCT protocols, Song et al. report XVI protocols to have average doses in the range of 1 to 35 mGy using a similar measurement methodology to that utilized in this article.²⁰ The weighted average dose, *D_w*, from our LD-CBCT was 0.7 mGy, therefore justifying the designation of this protocol as an LD-CBCT protocol.

With respect to adequacy of the images for patient positioning, we found that measures of positional uncertainty were reasonably small and comparable or less than published reports in adults. For example, in a study comparing interfraction positioning uncertainties using 4 different thermoplastic immobilization devices in adult CNS IGRT with CBCT, Tryggstad et al. noted that mean VM for random interfraction error was 1.4 to 1.9 mm across devices.¹⁸ By comparison, our (within patient) interfraction error was similar, with a VM of 1.5 mm

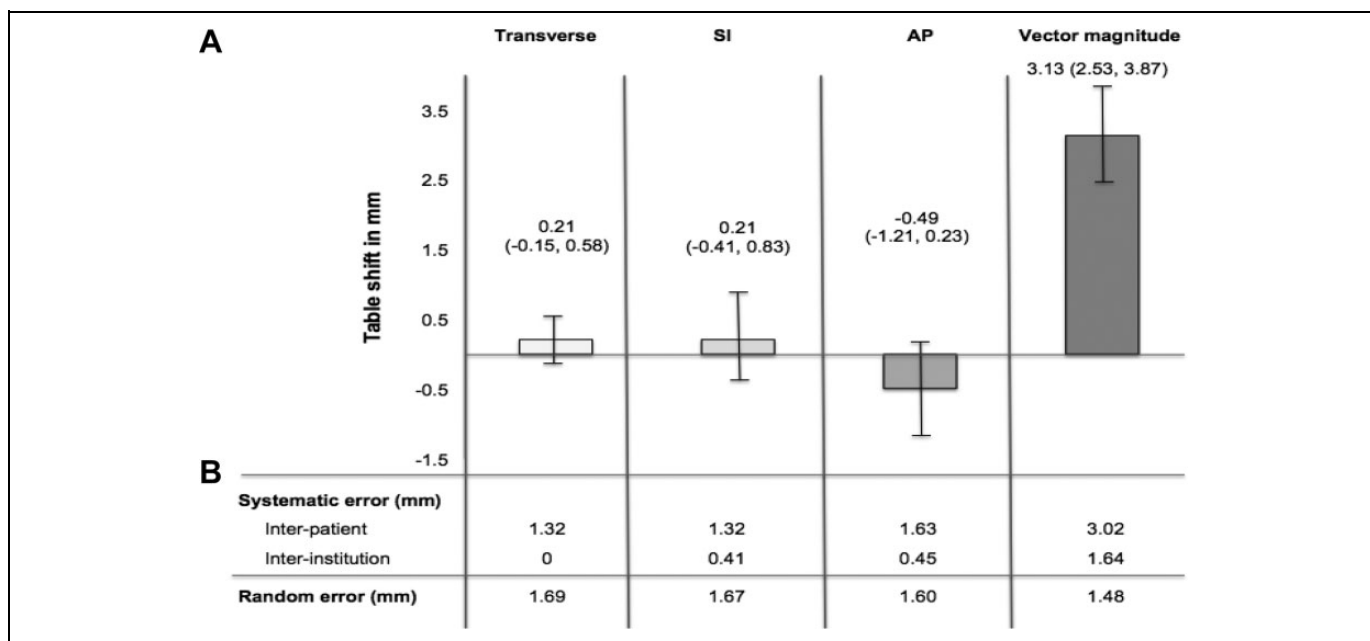


Figure 1. Group mean, systematic, and random error estimates between setup with laser alignment alone versus with cone-beam computed tomography (CBCT) in pediatric central nervous system (CNS) image-guided radiotherapy. A, Group mean error and 95% confidence intervals. B, Estimates of systemic and random error estimates. Table shifts between laser alignment and CBCT were measured in transverse = x , superior–inferior (SI) = y , and anterior–posterior (AP) = z translational directions. Vector magnitude (VM) was calculated as $\sqrt{(x^2 + y^2 + z^2)}$.

using the LD-CBCT. Additional studies of adult CNS and head and neck IGRT with thermoplastic mask immobilization report group mean VM ranging from 2.9 to 4.7 mm,^{21–23} again similar to the group mean VM in our study. Although there are likely differences in specific immobilization details, rate of anesthesia use, and KPS between the adult and pediatric populations, these data suggest that setup with LD-CBCT is similar to setup with standard-dose protocols.

Of note, the VM for group mean error in our study was estimated at approximately 3 mm. Since 3 mm was also the minimum CTV-to-PTV expansion used among consortium members, this suggests that a portion of patients evaluated would have setup within the CTV-to-PTV margins using LA alone. However, on univariate analysis, we found no significant predictors of setup accuracy (as estimated by mean VM). Therefore, we did not identify any patient demographics or treatment characteristics that would support altering IGRT practice patterns for patient subpopulations. Moreover, the 95% CIs for VM were relatively broad—for example, ranging from 1.4 to 6.2 mm for infratentorial tumors. The clinical significance of requiring a shift greater than 6 mm from initial setup with LA alone is noteworthy, particularly given proximity to critical and sensitive structures such as the brainstem in this location. In such cases, the risks associated with excess radiation dose from daily CBCT would likely weigh favorably against the risk of inadvertent exposure to adjacent normal tissue. Additionally, given the lower dose associated with the current protocol, the effects of excess dose from CBCT is likely further mitigated.

One criticism of this work may be that relative image quality and positioning uncertainty could conceivably be affected by patient size, raising the question if the current LD-CBCT protocol is indeed optimized for the target population. To address this concern, we conducted a post hoc analysis of cranial volume for a subset of patients in this study. Interestingly, the subgroup analysis did not find a significant correlation between cranial volume and age in a group of pediatrics ranging from 3 to 20 years. For comparison purposes only, pCT for 140 adults age >21 years who were treated using thermoplastic masks to brain sites at the Johns Hopkins University School of Medicine site was evaluated using the same methods for estimation of cranial volume. Among the adults, mean cranial volume was 12118.4 cm³ (SD 1486.2), with no statistical significance when compared to pediatrics by t test ($P = .285$; unpublished data). Corroborating the relative stability of cranial volume by age in our cohort is evidence that brain weight increases most dramatically from birth to age 3, with less substantial change thereafter.²⁴ These data suggest that standardized LD-CBCT protocols can be safely employed for CNS-directed IGRT across all age-groups ≥ 3 years.

Limitations of this study include the use of translational table shifts and VM as proxies for setup accuracy associated with LA compared to CBCT. As noted in the methods, a direct comparison between LD- and standard-dose protocols was not felt to be feasible given risks of excess radiation exposure in the pediatrics population. The validity of table shifts as a proxy for setup accuracy may be supported by consistency of this measure across treating institutions and as compared to the adult population noted above. Nonetheless, we do suggest caution in

Table 2. Univariate Analysis of Potential Predictors of Setup Accuracy^a for Pediatric CNS IGRT.

Variables ^b	VM in mm (95% CI)	P Value
Age		
>12 years	3.23 (2.66-3.91)	.91
≤ 12 years	3.26 (0.23-0.46)	
Gender		
Female	3.38 (0.69-16.4)	.79
Male	3.29 (2.62-4.15)	
Baseline KPS		
≥80	3.00 (2.50-3.60)	.28
<80	3.27 (2.37-4.50)	
Target location		
Supratentorial	3.21 (2.55-4.04)	.37
Infratentorial	2.95 (1.41-6.18)	
Extent of resection		
Gross residual disease	3.07 (2.34-4.02)	.49
No Gross residual disease	2.83 (1.10-7.29)	
Chemotherapy		
Prior or concurrent with IGRT	3.42 (2.63-4.44)	.50
No prior nor concurrent IGRT	3.10 (0.32-30.1)	
Baseline steroid use		
Yes	3.37 (2.90-3.91)	.22
No	3.06 (2.18-4.28)	
Anesthesia required		
Yes	3.08 (2.57-3.69)	.94
No	3.06 (2.38-3.95)	

Abbreviations: CBCT, cone-beam computed therapy; CI, confidence interval; CNS, central nervous system; IGRT, image-guided radiotherapy; KPS, Karnofsky Performance Status; VM, vector magnitude.

^aSetup accuracy is estimated by the VM of translational treatment table shifts between setup with laser alignment alone versus with CBCT.

^bModel does not converge when immobilization type was included.

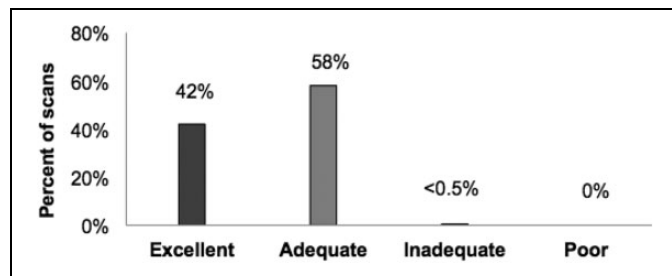


Figure 2. Physician rating of lower-dose cone-beam computed tomography (LD-CBCT) quality for tumor localization in pediatric image-guided central nervous system (CNS) radiotherapy (n = 173 LD-CBCT).

interpreting results rendered from this metric, as its internal and external validity has not been thoroughly characterized. Moreover, we were unable to directly compare positioning uncertainty data with a cohort of pediatrics treated using standard-dose CBCT at the consortium sites due to heterogeneity of standard dose protocols and inconsistent documentation of table shift data off of the protocol. As such, our comparisons were limited to published results from potentially similar adult populations. Again, in order to limit unnecessary radiation dose in this population, we were unable to repeat posttreatment

CBCT and were thus unable to account for intrafraction random error. Because of this, the group mean VM estimated by our study should not be misinterpreted as a margin prescription, as intrafraction error is included in most accepted margin recipes.¹⁹ Additionally, although the LD-CBCT protocol was uniform across institutions, other treatment practices may vary and skew the results. However, we found that interpatient error accounted for 65% of variability in the model, whereas inter-institution error accounted for significantly less (19% of variability). This suggests that the results had greater dependence on differences between patients than on differences between institutions. As such, these data support the use of LD-CBCT across a range of institutions—both in the United States and abroad. Finally, while our analyses suggest similar results with use of our LD-CBCT across a range of pediatrics and adults, it was out of the scope of the current study to compare various LD-CBCT dosing options to determine the optimal CBCT protocol in this setting.

Conclusions

In conclusion, our results suggest that LD-CBCT is likely adequate for target localization in pediatric CNS radiotherapy. Moreover, there are no clear patient characteristics that predict setup accuracy, suggesting that LD-CBCT may be appropriate across a wide range of patients and institutions. Given the success of the LD-CBCT protocol in pediatric CNS radiotherapy, next steps include extension of this protocol to other disease sites in pediatrics. Additionally, given similar practices for patient alignment and target localization, a study of the utility of LD-CBCT in adult CNS IGRT is also warranted. Lastly, further studies are needed to determine the threshold for the lowest possible dose required for adequate setup with CBCT and the clinical scenarios that may necessitate use of specific imaging protocols.

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Declaration of Conflicting Interests



The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Statement

This study was approved by the Institutional Review Board (IRB) (NA_00083758) at the Johns Hopkins School of Medicine. The IRB granted an exemption to obtain written or oral consent for this study because the use of low-dose cone-beam computed tomography scan is considered to be a standard of care for image-guided radiation treatment.

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ORCID iDSara R. Alcorn  <https://orcid.org/0000-0003-4620-5047>Stephanie A. Terezakis  <https://orcid.org/0000-0002-8125-3987>**Supplemental Material**

Supplemental material for this article is available online.

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