

## Research Letter

# An Analysis of Major Target Deviations in Craniospinal Irradiation Treatment Plans for Patients With Intermediate-Risk Medulloblastoma Within a Phase 3 Clinical Trial (Children's Oncology Group Study ACNS0331)



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Received September 6, 2022; accepted September 15, 2022

## Abstract

**Purpose:** Craniospinal irradiation remains an essential and yet difficult part of the treatment of patients with medulloblastoma. Whereas technological advances offer promise of increased conformity, reliance on advanced technology is not without risk, and it remains critical to carefully delineate targets. We describe examples of target deviations (TDs) in craniospinal irradiation treatment plans for postoperative patients with medulloblastoma in a phase 3 clinical trial (ACNS 0331).

**Methods and Materials:** The principal investigator independently performed a review of the treatment plans and portal films of enrolled patients and evaluated the plans for TDs. TDs of dose, dose uniformity, and volume were defined as major or minor deviations. Major TDs scored as protocol violations. The effect of major TDs on event-free survival (EFS) and overall survival (OS) was evaluated using the stratified Cox proportional hazards model.

**Results:** Of the 549 patients enrolled, 461 were available for this analysis. Thirty-two (7%) plans did not have data sufficient for TD evaluation. Major TDs were found in 32 of the 461 plans (7%). Of those, 21 were deviations of target volume alone, 7 were deviations of target dose alone, and 4 were deviations of both target volume and dose. The 25 patients with TDs of volume involved 29 sites. The

Sources of support: ACNS 0331 was supported by National Clinical Trials Network Operations Center Grant U10CA180886 and National Clinical Trials Network Statistics & Data Center Grant U10CA180899.

Disclosures: Dr Michalski reports that financial support was provided by the Children's Oncology Group (COG) and the National Cancer Institute. Dr Perkins reports a relationship with Mevion Medical Systems that includes consulting or advisory membership. Dr Lee is a data safety monitoring board member of the North American Consortium for Histiocytosis. Dr Perkins is a data safety monitoring board member for Mevion Medical Systems. Dr Fitzgerald is the principal investigator on the National Clinical Trials Network grant to University of Massachusetts Chan for Imaging and Radiation Oncology Core, which supports imaging and radiation therapy services to COG including the ACNS 0331 study (Grant No. 1 U24 CA180803). Dr Michalski reports support for this article from COG, grants from COG, and support for attending meetings and/or travel from COG. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Research data are stored in a Children's Oncology Group repository and will be shared upon request to the corresponding author.

Clinical trial information: Children's Oncology Group ACNS 0331 is a phase 3 double-randomized trial evaluating limited target volume boost irradiation and reduced dose craniospinal radiation therapy (18 Gy) and chemotherapy in children with newly diagnosed standard risk medulloblastoma.

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<https://doi.org/10.1016/j.adro.2022.101083>

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most common major TDs of volume involved the brain (9 of 29) and the posterior fossa (9 of 29). On Cox proportional hazards modeling, the presence of a major TD did not statistically significantly affect EFS (hazard ratio, 0.98; 95% confidence interval, 0.45-2.11;  $P = .9541$ ) or OS (hazard ratio, 1.10; 95% confidence interval, 0.51-2.38;  $P = .8113$ ).

**Conclusions:** Although intensity modulated radiation therapy and proton therapy are promising in improving conformity and sparing organs at risk, technology does not substitute for careful anatomic definition of target volumes. The study was not powered to evaluate the effect of TDs on EFS and OS; therefore, the statistical analysis presented in this study must be interpreted with caution.

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## Introduction

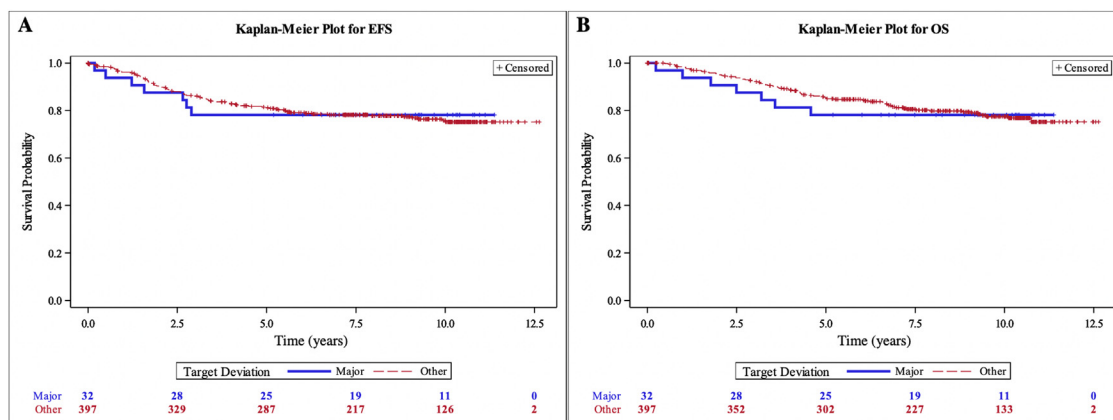
Postoperative craniospinal irradiation (CSI) remains a mainstay in the treatment of medulloblastoma and presents as one of the more challenging techniques to master in radiation oncology.<sup>1-4</sup> Studies have shown that high technical quality is essential to properly treat all potential metastatic deposits within the craniospinal axis.<sup>3,5,6</sup> Carrie et al demonstrated a correlation between tumor relapse and target deviations (TDs).<sup>5</sup> Similarly, Miralbell et al demonstrated a correlation between whole brain irradiation field correctness and supratentorial failure-free survival.<sup>6</sup>

With the advent of new technology has come a variety of promising methods with which to treat the craniospinal axis.<sup>7</sup> Technological advances such as intensity modulated radiation therapy (IMRT), tomotherapy, and proton therapy (PT) as well as improved setup techniques such as supine positioning have all shown substantial promise in more specifically targeting the treatment field and limiting the dose to the surrounding organs at risk (OARs) compared with conventional CSI.<sup>8-14</sup> However, these techniques are not without risk. Noble et al compared PT and helical IMRT with standard therapies and noted that although the PT and helical IMRT plans were more conformal, they tended to underdose the posterior fossa, and helical IMRT CSI could induce a higher risk of secondary malignancies in pediatric patients.<sup>15</sup>

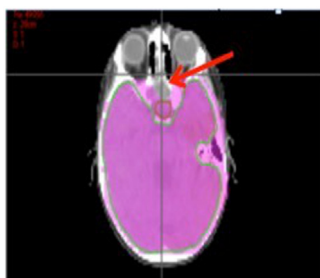
It is clear that although technological advances show great promise in the delivery of CSI, innovation cannot come at the price of subpar technique and attention to detail. Tarbell et al described the appropriate dose and volume of CSI, which must include the whole brain and spinal contents with a boost to the posterior fossa.<sup>16</sup> We provide examples of initially missed or underdosed CSI volumes in patients in ACNS0331 (NCT00085735), a phase 3 clinical trial investigating the efficacy of reduced dose and volume radiation therapy with chemotherapy in patients with newly diagnosed average-risk medulloblastoma,<sup>17</sup> as well as a statistical analysis of the effect of major TDs on event-free survival (EFS) and overall survival (OS).

## Methods and Materials

The principal investigator (PI) of ACNS0331 independently performed a review of the treatment plans and portal films of enrolled patients and evaluated the plans for TDs. Of note, per protocol, all patients underwent a pretreatment review of their boost treatment plans and an on-treatment review of their CSI treatment plans separate from the independent PI review. The dosing guidelines for these patients were as follows. Children 3 to 21 years of age were randomized to standard-dose (23.4 Gy) or low-dose CSI (18 Gy). Next, all children were randomized to a whole posterior



**Figure 1** Event-free survival (EFS) and overall survival (OS). The Kaplan-Meier method was used to estimate EFS (A) and OS (B), stratified by the presence of a major target deviation. There were 429 patients included in this analysis. Patients with insufficient data for plan evaluation were excluded.



**Figure 2** Craniospinal irradiation treatment plan, axial image. An axial image from a treatment plan at the level of the cribriform plate. The red arrow indicates the partially missed cribriform plate.

fossa boost or a limited involved field boost to a cumulative dose of 54 Gy. Younger children (ages 3-7 years) who received the limited involved field boost received an additional 5.4-Gy whole posterior fossa boost.

The clinical target volume (CTV) in the study was the entire craniospinal axis. The whole-brain field was intended to extend anteriorly to include the entire frontal lobe and cribriform plate. Inferiorly, the CTV had to extend below the base of skull to the foramen magnum. The spinal target volume was to encompass the entire thecal sac. Finally, the posterior fossa boost CTV extended inferiorly from the C1 vertebral canal through the foramen magnum, laterally to the bony walls of the occiput and temporal bones, and superiorly to the tentorium cerebelli.

A major TD of prescription dose was defined as a dose differing by more than 10% of the protocol specified dose in the brain and spine fields. For the boost field, a major TD of prescription dose was defined as less than 90% of the prescribed dose covering at least 95% of the planning target volume (PTV) and/or <48 Gy covering 100% of the PTV. A major TD of dose uniformity was defined as a variation of dose in a target volume exceeding  $\pm 15\%$ . A major TD of volume occurred when a tumor or potential

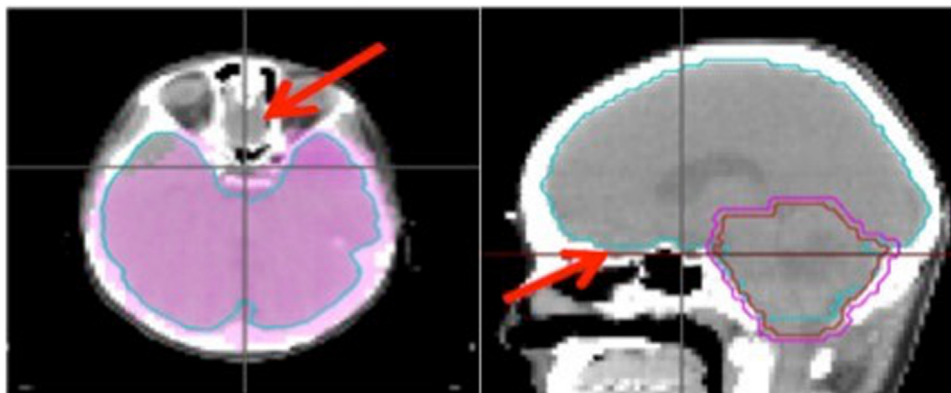
tumor-bearing area was transected or if there was a major incorrect definition of an OAR or target. These definitions were stipulated per the study protocol.<sup>17</sup> Further details of the methods and materials of this study can be accessed in the primary publication and study protocol.<sup>17</sup>

Descriptive statistics, frequency, and percentage for nominal variables were calculated for demographic and baseline characteristic variables by TD. For group comparisons, the *P* value of nominal variables was derived from the Pearson  $\chi^2$  exact test; the *P* value of numeric values was derived from the independent *t* test. EFS was calculated from the date of study entry to the date of disease progression, recurrence, second malignant neoplasm, or death from any cause, whichever occurred first or to the date of the last follow-up. OS was calculated from the date of study entry to the date of death from any cause or to the date of the last follow-up. EFS and OS were estimated using the Kaplan-Meier method.

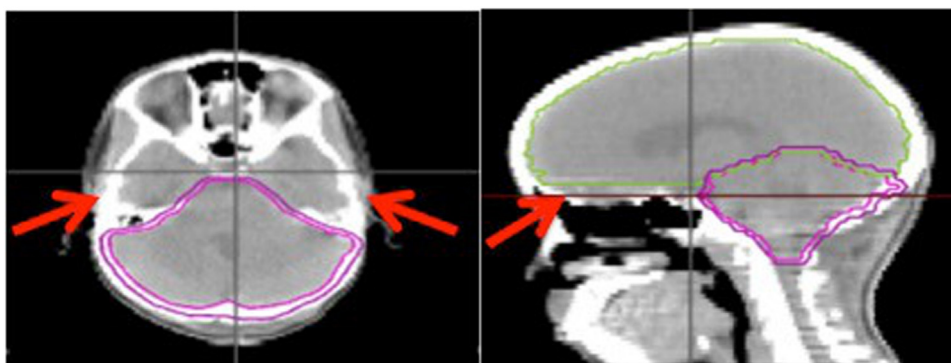
The stratified log-rank test was used for comparison between groups, and the stratified Cox proportional hazard models were built to estimate the hazard ratios between groups for both EFS and OS. The 3 CSI age groups (3-7 years with low-dose CSI, 3-7 years with standard-dose CSI, and 8-21 years with standard-dose CSI) were used as the stratified factors in the stratified log-rank test and stratified Cox proportional hazard models. Without specification, all statistical tests are 2-sided. The data analysis was conducted with SAS 9.4.

## Results

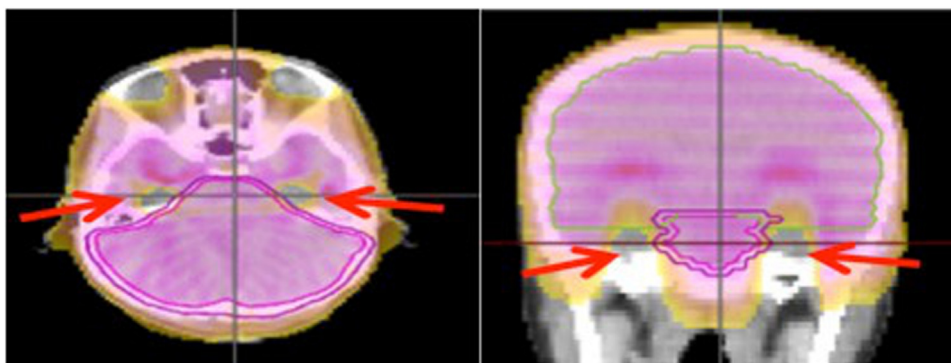
The study initially enrolled 549 patients. Thirty-six patients were deemed ineligible upon review by the study chair, and 42 patients were found to have excess residual or disseminated disease upon central review. Seven patients were found to have anaplasia upon central pathology review, and 3 patients did not have data



**Figure 3** Craniospinal irradiation treatment plan, axial and sagittal images. Axial and sagittal images from a plan that excluded the cribriform plate. The red arrow in each image indicates the entirely missed cribriform plate.



**Figure 4** Craniospinal irradiation treatment plan, axial and sagittal images. Axial and sagittal images from a plan that excluded both the cribriform plate and middle cranial fossa. In the axial image, it is apparent that both the cribriform plate and middle cranial fossa were missed in the treatment plan. The red arrow in each image indicates the missed portion of the middle posterior fossa.



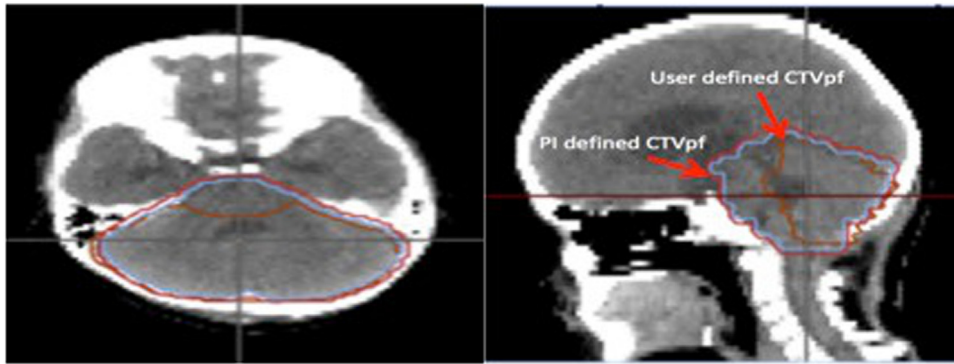
**Figure 5** Craniospinal irradiation treatment plan, axial and coronal images. Axial and coronal images from a treatment plan in which the temporal lobes are severely underdosed. Temporal lobe dosing requirements instruct the temporal lobes to receive a minimum of 18 Gy, which they clearly did not. The red arrow in each image indicates the underdosed portions of the temporal lobes.

available for this analysis. This yielded 461 enrolled and evaluable patients for this specific analysis for whom the PI independently reviewed the treatment plans and portal films of. Randomization data for these 461 patients are available in Table E1. The majority of plans (397 of 461; 86%) plans were deemed appropriate, including 112 plans with minor deviations. Major TDs were found in 32 of 478 (7%) plans and 32 of 478 (7%) were found to have insufficient data submitted for plan evaluation.

Of the 112 patients with minor TDs, 60 of 120 were deviations of target dose alone, 40 of 120 were deviations of target volume alone, and 12 of 120 were deviations of both target volume and dose. Of the 32 patients with major TDs, 21 were deviations of target volume alone, 7 were deviations of target dose alone, and 4 were deviations of both target volume and dose. The 25 patients with major TDs of volume involved 29 different sites within the craniospinal axis. Nine

of 29 involved the posterior fossa target volume, 9 of 29 involved the brain volume, 7 of 29 involved the spine volume, and 4 of 29 involved the boost volume. On Cox proportional hazards modeling, the presence of a major TD did not statistically significantly affect EFS (hazard ratio, 0.98; 95% confidence interval, 0.45-2.11;  $P = .9541$ ) or OS (hazard ratio, 1.10; 95% confidence interval, 0.51-2.38;  $P = .8113$ ). Kaplan-Meier curves for EFS (Fig. 1A) and OS (Fig. 1B) stratified by the presence of a major TD or not are provided.

Examples of TDs in IMRT CSI plans are presented in Figs. 2 to 6. These include TDs of volume involving contouring errors excluding the cribriform plate (Figs. 2-4), middle cranial fossa (Fig. 5), and posterior fossa (Fig. 6) as well as TDs of dose leading to underdosing of the temporal lobes (Fig. 4). Each of these scored as a major TD. These areas may be overlooked in traditional CSI treatment planning and still receive near prescription dose but require careful delineation in IMRT CSI plans.



**Figure 6** Craniospinal irradiation treatment plan, axial and sagittal images. Axial and sagittal images from a whole posterior fossa treatment. As indicated in the image, the brain stem has been excluded in the submitted clinical target volume (CTV). The original CTV of the posterior fossa (brown line; user-defined CTVpf) and the CTV of the posterior fossa created by the principal investigator (red line; principal investigator–defined CTVpf) in review are labeled as such. CTVpf = CTV of the posterior fossa.

## Discussion

We showcase several examples from a modern clinical trial in which treatment plans for patients with medulloblastoma either grossly underdosed or entirely missed the cribriform plate, middle cranial fossa, temporal lobes, or brain stem. These are unacceptable errors in treatment planning that may have grave consequences.<sup>18-20</sup> For example, it has been previously reported that exclusion of the cribriform plate in CSI leads to an increased rate of supratentorial failures.<sup>18</sup> In a French Society of Pediatric Oncology study of reduced-dose craniospinal irradiation in patients with average-risk medulloblastoma, major radiation therapy protocol violations correlated with treatment failure.<sup>19</sup> Although the presence of a major TD did not affect EFS or OS on Cox proportional hazards modeling in this study, the study was not powered to evaluate this endpoint, and therefore this should be interpreted with care. The overall number of major TDs in this study was quite low at 7% of cases, compared with an approximately 15% to 30% major TD rate seen in prior studies.<sup>3-5</sup> The low event rate further compounds the challenge in statistically analyzing this data.

Although IMRT and PT are promising in improving CSI conformity and sparing OARs, technology does not preclude careful anatomic definition of target volumes. Ironically, even inaccurate contours may yield a good dose-volume histograms, which appears to meet OAR constraints. In the example displayed in Fig. 5, the treating physician was clearly attempting to spare the cochlea, one of the goals of the advanced techniques on this clinical trial. The dose-volume histogram review did suggest good coverage of the supratentorial brain and sparing of the cochlea, but the anatomic review of the dose distribution demonstrated a geographic miss that would not be detected by typical verification films.

The primary outcome results of this phase 3 clinic trial underscore the critical importance of accurate target delineation.<sup>17</sup> In the study, children treated with low-dose CSI had an inferior EFS compared with patients treated with standard-dose CSI (71.4% vs 82.9% at 5 years). This suggests that if a patient was to be underdosed due to a target deviation, it may predispose them to an inferior outcome.

## Conclusion

This descriptive and statistical analysis is meant to serve as a reminder that despite the implementation of advanced technology, careful anatomic definition of target volumes remains critically important. Although major TDs did not affect EFS or OS in this study, this protocol was not powered to evaluate this endpoint.

## Acknowledgments

This project was conducted and written under the supervision of the Children's Oncology Group (COG), supported by National Clinical Trials Network Operations Center Grant U10CA180886 and National Clinical Trials Network Statistics & Data Center Grant U10CA180899. COG Study ACNS0331 was also supported by the St. Baldrick's Foundation.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.adro.2022.101083](https://doi.org/10.1016/j.adro.2022.101083).

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