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

Short title: CSI Target Deviations in ACNS 0331

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**Clinical trial information:** COG ACNS 0331 is a phase III double randomized trial evaluating limited target volume boost irradiation and reduced dose craniospinal radiotherapy (18Gy) and chemotherapy in children with newly diagnosed standard risk medulloblastoma.

**Data availability statement:** Research data are stored in a COG repository and will be shared upon request to the corresponding author.

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**Introduction:** Craniospinal irradiation (CSI) remains an essential and yet difficult part of the treatment of medulloblastoma patients. While technological advances offer promise of increased conformity, it is not without risk, and it remains critical to carefully delineate targets. We describe examples of target deviations (TDs) in CSI treatment plans for post-operative medulloblastoma patients in a phase III clinical trial (ACNS XXXX).

**Methods and Materials:** The principal investigator independently performed a review of the treatment plans and portal films of enrolled subjects and evaluated the plans for TDs. Target deviations of dose, dose uniformity, and volume were defined as major or minor deviations. Major TDs scored as protocol violations. The impact 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 subjects were available for this analysis. 32
(7%) plans did not have data sufficient for TD evaluation. Major TDs were found in
32/461 (7%) plans. 21/32 were deviations of target volume alone, 7/32 were deviations of
target dose alone, and 4/32 were deviations of both target volume and dose. The 25
patients with TDs of volume involved 29 sites. The most common major TDs of volume
involved the brain (9/29) and the posterior fossa (9/29). On Cox proportional hazards
modeling, the presence of a major TD did not statistically significantly impact EFS
(HR=0.98, 95% CI 0.45-2.11, p=0.9541) or OS (HR=1.10, 95% CI 0.51-2.38, p=0.8113).

**Conclusion:** While intensity modulated radiation therapy and proton therapy are
promising in improving conformity and sparing organs at risk, technology does not
substitute for careful anatomical definition of target volumes. The study was not powered
to evaluate the impact of TDs on EFS and OS, and therefore the statistical analysis
presented in this study must be interpreted with caution.
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.1–4 Studies have shown that high technical quality is essential to properly treat all potential metastatic deposits within the craniospinal axis.3,5,6 Carrie et al demonstrated a correlation between tumor relapse and target deviations (TDs).5 Similarly, Miralbell et al demonstrated a correlation between whole brain irradiation field correctness and supratentorial failure-free survival.6

With the advent of new technology have come a variety of promising methods with which to treat the craniospinal axis.7 Technologic advances such as intensity-
modulated radiation therapy (IMRT), tomotherapy, and proton therapy (PT) as well as improved set up 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) when compared to conventional CSI.\textsuperscript{8–14} However, these techniques are not without risk. Noble et al compared PT and helical IMRT to standard therapies and noted that while the PT and helical IMRT plans were more conformal, they tended to under dose the posterior helical IMRT CSI could induce a higher risk of secondary malignancies in pediatric patients.\textsuperscript{15}

It is clear that while technological advances show great promise in the delivery of CSI, innovation cannot come at the price of sub-par technique and attention to detail. Tarbell et al described the appropriate dose and volume ofCSI, which must include the whole brain and spinal contents with a boost to the posterior fossa.\textsuperscript{16} We provide examples of initially missed or underdosed CSI volumes in patients in ACNSXXXX (NCTXXX), a phase III clinical trial investigating the efficacy of reduced dose and volume radiotherapy with chemotherapy in newly diagnosed average-risk medulloblastoma patients,\textsuperscript{17} as well as a statistical analysis of the impact of major TDs on event-free survival (EFS) and overall survival (OS).

**Methods and Materials**

The principal investigator (PI) of ACNSXXXX independently performed a review of the treatment plans and portal films of enrolled subjects and evaluated the plans for TDs. Of note, per protocol all patients underwent a pre-treatment 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
age 3 to 21 were randomized to standard-dose, 23.4Gy, or low-dose CSI, 18Gy. Next, all children were randomized to a whole posterior fossa boost or a limited involved field boost to a cumulative dose of 54Gy. Younger children age 3 to 7 whom received the limited involved field boost received an additional 5.4Gy 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 covers at least 95% of the planning target volume (PTV) and/or <48Gy covers 100% of the PTV. A major TD of dose uniformity was defined as a variation of dose in a target volume exceeding +/-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. Further details of the methods and materials of this study can be accessed in the primary publication and study protocol.

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-Square 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 (SMN), 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 three age-CSI groups (age 3 to 7 years with low dose CSI, age 3 to 7 years with standard dose CSI, and age 8 to 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 two-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 three patients did not have data available for this analysis. This yielded 461 enrolled and evaluable subjects 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 Supplementary Table 1. The
majority of plans (397/461; 86%) plans were deemed appropriate, including 112 plans with minor deviations. Major TDs were found in 32/478 (7%) plans and 32/478 (7%) were found to have insufficient data submitted for plan evaluation.

Of the 112 patients with minor TDs, 60/120 were deviations of target dose alone, 40/120 were deviations of target volume alone, and 12/120 were deviations of both target volume and dose. Of the 32 patients with major TDs, 21/32 were deviations of target volume alone, 7/32 were deviations of target dose alone, and 4/32 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 twenty-nine involved the posterior fossa target volume, 9/29 involved the brain volume, 7/29 involved the spine volume, and 4/29 involved the boost volume. On Cox proportional hazards modeling, the presence of a major TD did not statistically significantly impact EFS (HR=0.98, 95% CI 0.45-2.11, p=0.9541) or OS (HR=1.10, 95% CI 0.51-2.38, p=0.8113). Kaplan-Meier curves for EFS (Figure 1A) and OS (Figure 1B) stratified by the presence of a major TD or not are provided.

Examples of TDs in IMRT CSI plans are presented in Figures 2-6. These include TDs of volume involving contouring errors excluding the cribriform plate (Figures 2-4), middle cranial fossa (Figure 5), and posterior fossa (Figure 6) as well as TDs of dose leading to underdosing of the temporal lobes (Figure 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.

Discussion
We have showcased 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 brainstem. These are unacceptable errors in treatment planning that may have grave consequences.\textsuperscript{18–20} For example, it has been previously reported that exclusion of the cribriform plate in CSI leads to an increased rate of supratentorial failures.\textsuperscript{18} In a French Society of Pediatric Oncology study of reduced dose craniospinal irradiation in average risk medulloblastoma patients, major radiotherapy protocol violations correlated with treatment failure.\textsuperscript{19} While the presence of a major TD did not impact 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 15-30\% major TD rate seen in prior studies.\textsuperscript{3–5} The low event rate further compounds the challenge in statistically analyzing this data.

While IMRT and PT are promising in improving CSI conformity and sparing OARs, technology does not preclude careful anatomical definition of target volumes. Ironically, even inaccurate contours may yield a good Dose-Volume histograms (DVH) which appears to meet OAR constraints. In the example displayed in Figure 5, the treating physician was clearly attempting to spare the cochlea, one of the goals of the advanced techniques on this clinical trial. The DVH 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 III clinic trial underscore the critical importance of accurate target delineation. In the study, children treated with low-dose CSI had an inferior event free survival compared to patients treated with standard-dose CSI (71.4% vs. 82.9% at five years). This suggests that if a patient were 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 reminder that in spite of the implementation of advanced technology, careful anatomic definition of target volumes remains critically important. While major TDs did not impact EFS or OS in this study, this protocol was not powered to evaluate this endpoint.

**References**


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Declaration of interests

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jeff Michalski reports financial support was provided by Children's Oncology Group. Jeff Michalski reports financial support was provided by National Cancer Institute. Stephanie Perkins reports a relationship with Mevion Medical Systems that includes: consulting or advisory. Conflicts of interest: Joshua P Schiff: none. Yimei Lee: Data Safety Monitoring or Advisory Board: DSMB member for North American Consortium for Histiocytosis. Yu Wang: none. Stephanie M Perkins: Data Safety Monitoring or Advisory Board: Mevion Medical Systems. Sandy Kessel: none. Thomas J Fitzgerald: Grants: PI on the NCTN grant to UMASS Chan for IROC which supports imaging and radiation therapy services to COG including the ACNS 0331 study (Grant #1 U24 CA180803). Nicole Larrier: none. Jeff M Michalski: Support for this manuscript: Children's Oncology Group; Grants: Children's Oncology Group; Support for attending meetings and/or travel: Children's Oncology Group.

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Figure Captions

1. **Figure 1. Event-free survival and overall survival.** The Kaplan-Meier method was used to estimate EFS (A) and OS (B), stratified by the presence of a major TD or not. There were 429 patients included in this analysis, as patients with insufficient data for plan evaluation were excluded from this analysis.

![Kaplan-Meier plots](image)

2. **Figure 2. CSI 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.

![Axial image](image)

3. **Figure 3. CSI 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.

![Axial and sagittal images](image)
4. **Figure 4. CSI treatment plan, axial and sagittal images.** Axial and sagittal images from a plan that excluded both the cribiform plate and middle cranial fossa. In the axial image it is apparent that both the cribiform 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.

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

6. **Figure 6. CSI 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 CTV. The original CTV of the posterior fossa (brown line; user defined CTVpf) and the CTV of the posterior fossa created by the PI (red line; PI defined CTVpf) in review are labeled as such.