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A Multi-Institution Prospective Trial of Reduced-Dose Craniospinal Irradiation (23.4 Gy) Followed by Conformal Posterior Fossa (36 Gy) and Primary Site Irradiation (55.8 Gy) and Dose-Intensive Chemotherapy for Average-Risk Medulloblastoma

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Abstract

Purpose/Objective—Limiting neurocognitive sequelae of radiation therapy (RT) has been an objective in the treatment of medulloblastoma (MB). Conformal RT to less than the entire posterior fossa (PF) after craniospinal irradiation (CSI) may reduce neurocognitive sequelae and requires evaluation.

Materials/Methods—Between October 1996 and August 2003, 86 patients, 3–21 years of age, with newly diagnosed, average-risk MB were treated on a prospective, IRB-approved, multi-institution trial of risk-adapted RT and dose-intensive chemotherapy. RT began within 28 days of definitive surgery and consisted of CSI (23.4 Gy), conformal PF RT (36.0 Gy) and primary site RT (55.8 Gy). The planning target volume for the primary site included the post-operative tumor bed surrounded by an anatomically confined margin of 2 cm which was then expanded with a geometric margin of

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0.3-0.5 cm. Chemotherapy was initiated 6 weeks after RT and included 4 cycles of high-dose cyclophosphamide, cisplatin and vincristine.

Results—With a median follow-up of 61.2 months (5.2-115.0 months), the estimated 5-year event-free survival and cumulative incidence of PF failure were $83.0\% \pm 5.3\%$ and $4.9\% \pm 2.4\%$ ($\pm$ SE), respectively. Targeting guidelines used in this study resulted in a mean reduction of 13% in the volume of the PF receiving doses above 55Gy compared to conventionally planned RT. Reductions in dose to the temporal lobes, cochleae and hypothalamus were statistically significant.

Conclusions—This prospective trial demonstrates that irradiation of less than the entire PF after 23.4 Gy CSI for average-risk MB results in disease control comparable to treatment of the entire PF.

Keywords

Radiotherapy; conformal radiotherapy; chemotherapy; pediatrics; CNS neoplasm

INTRODUCTION

Comprehensive post-operative irradiation of the neuraxis and anatomic posterior fossa (PF) has been standard in the treatment of medulloblastoma (MB) for nearly 50 years¹⁻³ and the quality of treatment, including radiation dose and volume, has a significant impact on outcome.⁴⁻⁶ Long-term survivors experience a spectrum of radiation-related treatment effects including hearing loss,⁷ endocrine deficiencies,⁸ somatic effects,⁹ cognitive decline,¹⁰ cerebrovascular damage^{11,12} and secondary malignancies.¹³ Measures have been taken to lessen the effects of radiation therapy for patients who have favorable outcomes including those with average-risk MB¹⁴ defined as no evidence of neuraxis dissemination, a minimal amount of residual tumor and no evidence of brainstem invasion or transtentorial extension from the primary site.

Lowering the neuraxis dose from the traditional 36 Gy has been an important goal for investigators and was accomplished with the addition of combination chemotherapy after craniospinal irradiation (CSI) to 23.4 Gy.^{15,16} The evolved standard for average-risk MB in North America includes post-operative CSI to 23.4 Gy, irradiation of the anatomic PF to 55.8 Gy and 12 months of combination chemotherapy as evidenced by the recently completed trial of the Children's Oncology Group.¹⁷ Reducing the neuraxis dose in the absence of chemotherapy has met with limited success¹⁸ and attempts to further reduce the neuraxis dose to 18 Gy with chemotherapy have not been made in a large prospective trial.¹⁹

Despite the use of chemotherapy and neuraxis dose reductions, decline in cognitive function continues to be significant,²⁰ leading investigators to consider new ways to further reduce the side effects of radiation therapy. Several approaches have been taken including reduction of the neuraxis dose to 18 Gy,²¹ supplementing lower dose CSI with radiolabeled antibodies²² and targeting less than the entire PF for the boost phase of therapy.²³⁻²⁵ Considering that conventional treatment of the entire PF²⁶ will irradiate 35% of the entire brain and 60% of either temporal lobe,²⁷ reassessing the role of PF irradiation, developing new targeting guidelines to limit the boost volume to the tumor bed and testing newer methods to plan and deliver radiation therapy appear to provide the greatest opportunity to reduce the effects of irradiation.

From 1996 through 2003 we conducted a multi-institutional study of risk-adapted radiation therapy and dose-intensive chemotherapy with peripheral stem cell support for children ages 3-21 years with MB. Average-risk patients received CSI to 23.4 Gy, conformal PF irradiation to 36 Gy and conformal primary site irradiation to 55.8 Gy followed by four cycles of high-dose chemotherapy. The primary aim was to incrementally reduce the volume that received the prescription dose of 55.8 Gy without affecting the rate or pattern of failure. The secondary

aim was to reduce side effects of treatment and patients were prospectively monitored for cognitive decline. In a recent report, we described the event free survival for these patients as a subgroup of a larger study for patients with medulloblastoma. Therein, we report the local control, event free survival and relevant dosimetry for these patients.²⁸

This study is the largest prospective series that includes patients treated with less than entire PF irradiation and represents a small but important step in further reducing the side effects of irradiation. The results reported provide a framework for further volume reduction in these patients and important insight and considerations in attempting to treat patients using newer guidelines.

MATERIALS AND METHODS

Patients

From October 1996 through August 2003, 86 pediatric patients with average-risk MB were enrolled on a multi-institution trial of risk-adapted radiation therapy and dose-intensive chemotherapy with peripheral stem cell support approved by the institutional review boards of the collaborating institutions that included St. Jude Children's Research Hospital in Memphis, Tennessee, Texas Children's Hospital in Houston, Texas, Royal Children's Hospital in Melbourne, Australia and The New Children's Hospital in Sydney, Australia. The median age was 8.7 years, range 3.1 – 20.1 yrs. Criteria for average-risk classification included age between 3 and 21 years; histologic confirmation of MB; residual tumor less than 1.5 cm²; Chang stage T1-T3b;²⁹ no evidence of dissemination by MRI of the brain and spine or CSF cytology; no prior radiation or chemotherapy; score of 0-3 on the Eastern Cooperative Oncology Group performance scale; Informed consent was obtained from all patients, parents, or legal guardians.

Extent of Resection Definitions

All patients underwent resection prior to radiation therapy. Gross-total resection (GTR) was recorded when the only tumor cells that remained were visible with the use of the operating microscope; GTR patients had no evidence of disease on postoperative neuroimaging. Near-total resection (NTR) was > 90% resection visible on postoperative neuroimaging. Second surgery was used to maximize the extent of resection before irradiation. GTR was achieved in 77, and NTR in 9 patients.

Radiation Therapy

All patients received 23.4 Gy CSI, PF irradiation to 36 Gy and primary site irradiation to 55.8 Gy using conformal techniques. CSI was initiated within 28 days of maximal resection and followed local institutional guidelines regarding technique. The CSI volume included the subarachnoid volume with special attention to the inclusion of the cribriform plate and temporal fossae; the full width of the spinal subarachnoid space, and the inferior aspect of the thecal sac. CSI dosimetry was measured at the midplane of the cranial volume and at the posterior border of the vertebral body for the spinal field(s). Efforts were made to minimize inhomogeneity at the craniocervical junction and the dose gradient across the spinal cord. Definitions for the target volumes and treatment dosimetry adhered closely to the ICRU Report 50.³⁰

The clinical target volume (CTV) for the posterior fossa volume included the entire infratentorial volume. The planning target volume (PTV) for the posterior fossa included an additional margin of 0.5 cm to account for uncertainty in immobilization and daily patient positioning. The primary site was irradiated after the PF. The primary site had a gross tumor volume (GTV), CTV, and PTV. The GTV included all gross residual tumor and/or the tumor bed at the primary site based on the initial pre-operative MR imaging examination that defined

the tissues initially involved with disease and the post-operative MR imaging examinations that identified residual disease and/or the tumor bed. The GTV in most cases was a contracted or collapsed tumor bed. Tissue defects resulting from surgical approaches were not included as part of the GTV. The CTV included the GTV with an added margin of 2.0 cm that was meant to treat subclinical microscopic disease and was anatomically confined (i.e., the CTV was limited to the confines of the bony calvarium, falx and tentorium where applicable or extended up to but not beyond neuroanatomic structures through which tumor extension or invasion was certain not to have occurred). When the GTV approached the boundary of a compartment, the CTV extended to and included the boundary. The 2 cm CTV margin was chosen based on prior experience²³ and margins used to define the target volumes for CNS embryonal tumors in a number of prior cooperative group trials. The PTV included a margin of 0.5 cm added to the CTV in 3-dimensions. The PTV was a geometric expansion of the CTV. The purpose of the PTV was to account for uncertainty in immobilization, image registration and daily variability in patient positioning. Conventional fractionation (1.8 Gy per day) was used to treat all patients. For volume-based treatment plans, the entire PTV was encompassed within the 95% isodose surface and no more than 10% of the volume within this isodose surface received greater than 110% of the prescription dose. A small number of patients were treated with intensity-modulated radiation therapy using axial coplanar beams and a binary collimator for which lower isodose coverage was accepted.

The immobilization method was chosen by the local institution. Most patients were treated in the prone position using a vacuum-bag as the immobilization device. The head was extended for the CSI phase of treatment. The head was in the neutral position for the other phases of treatment. IV general anesthesia with supplemental oxygen and specialized monitoring was used in approximately 70% of children under the age of 7 years.

Chemotherapy

Chemotherapy, consisting of four 28-day cycles of high-dose cyclophosphamide, cisplatin, and vincristine, was initiated 6 weeks after radiation therapy. Each cycle was followed by bone marrow or stem cell rescue with the duration of chemotherapy planned for 16 weeks.³¹

Statistical Analysis

Event-free survival (EFS) and local control (LC) were estimated using the Kaplan-Meier³² method. The formula of Peto et al.³³ was used to calculate standard errors. Time at risk for estimation of EFS was calculated from study enrollment to the date of first event. An event was defined as progression, second malignancy, or death. Patients still alive were censored at the last follow-up date. Time at risk for estimation of LC was calculated from study enrollment to the date of posterior fossa failure. Patients were censored at the earliest date of distant failure, second malignancy, or death. Patients that were alive with no failure were censored at the last follow-up date.

The cumulative incidence of posterior fossa failure was estimated using the method described by Kalbfleisch and Prentice.³⁴ Time at risk was calculated from study enrollment to the date of posterior fossa failure or to the date of a competing event (progression in the neuraxis only, development of a second malignant disorder, death), or to the date of last contact for patients who were censored. Radiation dosimetry comparisons were made using a paired t-test. Important clinical characteristics and outcome are tabulated in Table 1 (Table1).

RESULTS

Disease Control

With a median follow-up of 5.1 years (range 0.4 to 9.6) the estimated 5-year event-free survival and local control rates were $83.0\% \pm 5.3\%$ and $94.7\% \pm 3.4\%$, respectively (Figure 1). The cumulative incidence of posterior fossa failure was $4.9\% \pm 2.4\%$ (Figure 2). A total of 13 patients progressed after treatment including 3 patients in the posterior fossa, one patient with combined posterior fossa and neuraxis failure and 9 patients who failed in the neuraxis with a median time to failure of 2.0 years. Because of the limited number of failures, no risk-factors could be identified from specific clinical or treatment-related characteristics for the patients included in the study.

Treatment Volumes

Three-dimensional treatment data were reviewed for 42 of the 86 patients. The mean volumes for the GTV, CTV, PTV and posterior fossa were determined to be 19 ± 14 ml, 97 ± 40 ml, 161 ± 57 ml and 177 ± 37 ml, respectively (Figure 3). There was no statistically significant difference between the mean volumes of the PTV and anatomic posterior fossa. The dosimetry was reviewed for the same subset of patients. The mean percent volume of the posterior fossa receiving more than 55 Gy was $87\% \pm 13\%$. To provide a comparison between conventional posterior fossa and irradiation as performed in this study, the same patients were replanned with the posterior fossa PTV targeted with parallel-opposed lateral portals using 6 MV photons. Mean dose comparisons for specific normal tissue volumes (Figure 4) showed statistically significantly lower mean doses for temporal lobes ($p < 0.001$), cochleae ($p < 0.001$), brainstem ($p < 0.003$) and hypothalamus ($p = 0.016$). A significant increase in the mean dose to the total brain volume was noted ($p = 0.008$).

DISCUSSION

Treatment of less than the entire PF after 23.4 Gy CSI (tumor bed with limited margin of 2 cm) using conformal treatment methods is as effective as treatment of the entire PF based on the results from this prospective trial that included 86 children treated at participating centers. The 5 year event-free survival of $83.0\% \pm 5.3\%$ and 5 year cumulative incidence of local failure of 4.9% is similar to results reported for similar patients treated with 23.4 Gy CSI and adjuvant chemotherapy where the entire posterior fossa was irradiated to 55.8 Gy.¹⁵⁻¹⁷

The targeting guidelines for this study, in addition to 23.4 Gy CSI, included irradiation of the anatomic PF to 36 Gy and treatment of the postoperative tumor bed with a margin of 2cm to 55.8 Gy. These guidelines were responsible for a reduction in the volume of the PF receiving the prescription dose, which averaged 13% and a lack of difference between the planning target volume and the volume of the PF which were not statistically different.

Despite the modest dose reduction to the PF and lack of difference between the planning target and PF volumes, there was a statistically significant reduction in the mean dose to the temporal lobes, cochleae and hypothalamus based on the conformal treatment approach. The mean dose to the total brain increased which can be explained by the increase in dose heterogeneity and the larger volume receiving lower doses which is characteristic of conformal treatment methods.³⁵

The results of this study represent a small but significant step in the treatment of MB and provide a basis for further dose reductions in these patients. Our current trial includes further reductions in dose and volume: patients with average risk MB now receive 23.4 Gy CSI followed by treatment of the primary site using a 1 cm clinical target volume margin and the

same chemotherapy. We estimate that these newer guidelines will reduce the volume of the PF receiving the prescription dose by 28% compared to conventional irradiation.

The most recent national study sought to define the best chemotherapy regimen to accompany low-dose craniospinal irradiation and the standard posterior fossa boost.¹⁷ Based on the results reported here, analysis of the patterns of failure,³⁶ prior single institution experience using conformal treatment methods²³⁻²⁵ and limited data on the efficacy of 18.0 Gy CSI,¹⁹ attention has now turned to comparing 18.0 Gy and 23.4 Gy CSI and conventional boost treatment to treatment of less than the entire PF. A four-arm trial has been initiated by the Children's Oncology Group for pediatric patients between the ages of 3 and 8 years to definitively answer the important dose and volume reduction questions in a large multi-center randomized trial. For those older than 8 years, the craniospinal dose will remain 23.4 Gy with a comparison limited to the conventional posterior fossa boost and treatment of less than the entire posterior fossa.

Regardless of the guidelines chosen, radiation therapy for average risk medulloblastoma is technically demanding and at a minimum requires prophylactic treatment of the entire subarachnoid volume of the brain and spine and irradiation of the site at highest risk for recurrence in the posterior fossa. Ensuring that the prescribed dose of radiation is delivered to these volumes increases the likelihood of disease control.⁶ Only a decade ago the standard of care for all patients with MB was post-operative CSI to 36 Gy and boost treatment to 54-55.8 Gy using conventional fractionation of 1.8 Gy per day; chemotherapy was often not included. An attempt was made in a national study to lower the CSI dose to 23.4 Gy in average-risk patients in a randomized comparison with 36 Gy CSI. This study was closed early when interim analysis indicated an increased risk of relapse in patients receiving the reduced CSI dose.¹⁸ At the same time, disease control with multi-agent chemotherapy combined with reduced dose CSI was found to compare favorably with results achieved with standard dose CSI.¹⁵ This has now been adopted as the treatment standard for average-risk patients based on the promise that lower dose CSI would have fewer long term effects. Despite CSI dose reductions, cognitive impairment remains a significant concern with IQ loss of 4.3 points per year reported from a recent national trial of low-dose CSI and chemotherapy.²⁰ The multi-pronged approach by the Children's Oncology Group in their new trial, CSI dose reductions, elimination of the posterior fossa boost volume, and the use of conformal treatment methods and a new regimen of adjuvant chemotherapy will answer a number of important questions.

Investigators worldwide are testing different strategies to reduce treatment related toxicity employing hyperfractionated irradiation for both the CSI and boost phase.³⁷ The underlying principle is that smaller doses administered twice a day reduce long term effects. Hyperfractionation appears to be equally effective as once a day treatment provided the total dose is slightly increased. Comparing disease control and functional outcomes between different cooperative group strategies may some day provide the basis for a world-wide trial for patients with MB.

While reducing the CSI dose is helpful in reducing the dose to normal tissue volume such as the entire brain and temporal lobes, it does little to reduce the volume that receives the highest doses because the boost dose is prescribed to the entire PF.³⁸ Reducing the boost volume for average risk patients from the entire posterior fossa to the tumor bed with a limited margin has been recognized as an important means to reduce the normal tissue volume that receives the highest doses and does so without affecting the risk of increased neuraxis dissemination.

The risks associated with reducing the CSI dose and limiting the boost treatment to the post-operative tumor bed with a limited margin must be balanced against the observed effects of radiation therapy on cognition outcomes, neurologic function and growth and development.

Results from the trial reported herein show a decline in IQ of -2.4 points per year for children under the age of 7 years and -0.42 points per year for patients older than 7 years.³⁹ These neurocognitive data were derived from a report of 111 patients that included 74 of the 86 average-risk MB patients in the current study as well as 37 additional patients with high-risk MB. This compares favorably to contemporary patients treated with 23.4 Gy CSI and whole PF irradiation where a decline in IQ of 5.2 points per year was noted in patients younger than 7 years and similarly no change, or -0.8 pts per year, in patients older than 7 years.²⁰

Radiation dose-volume data can now be acquired for functional regions of the brain and correlated with outcome⁴⁰ and will lead to newer approaches in delivery and the analysis of outcomes. As the boost treatment of the primary site evolves from the PF to a volume approaching the post-operative tumor bed, radiation dosimetry will depend more on targeting guidelines, conformality of treatment and patient specific factors including the volume and location of the postoperative tumor bed. Models will be developed to predict side effects in patients with children based on treatment dosimetry and their accuracy will depend on the inclusion of patient and treatment related factors other than radiation dose and age. Patients with MB are known to develop a variety of cognitive deficits that are associated with specific functional subunits of the brain.^{41,42} These include the hippocampal regions of the temporal lobes that are intimately associated with the posterior fossa. Efforts to further restrict dose to the posterior fossa volume will have a direct impact on the distribution of dose to these structures. The next generation trials are now underway to test the safety of further volume reductions or the ability of proton beam radiation therapy to limit the cognitive decline in these patients.

The side effects attributed to radiation therapy have been a primary concern in the design of clinical trials for MB during the past two decades. The concern has been greatest for patients with average-risk MB, for whom long-term disease control is likely and the side effects have lasting impact. Systematically testing reductions in both the dose and volume of irradiation is an important contemporary strategy.

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Figure 1.
Event-free and overall survival for 86 pediatric patients with average-risk medulloblastoma treated with reduced-volume primary site irradiation.

Figure 2.
Cumulative incidence of posterior fossa failure for 86 pediatric patients with average-risk medulloblastoma treated with reduced-volume primary site irradiation.

Figure 3.

Target volumes for 42 pediatric patients with average-risk medulloblastoma treated with reduced-volume primary site irradiation. Mean gross-tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV) and posterior fossa volumes are presented.

Figure 4.
Comparison of mean doses to normal tissue volumes: conventional posterior fossa boost vs. present study (SJMB-96).

Table 1

Clinical and outcome characteristics for 86 pediatric patients with average-risk medulloblastoma treated with reduced primary site irradiation.

Age at Study Enrollment	Median	8.69
	Minimum	3.11
	Maximum	20.16
Sex		
F	N	33
	Percent	38.4
M	N	53
	Percent	61.6
Race		
Asian	N	2
	Percent	2.3
Black	N	11
	Percent	12.8
Hispanic	N	9
	Percent	10.5
Other	N	4
	Percent	4.7
White	N	60
	Percent	69.8
Surgery Extent		
Gross Total	N	77
	Percent	89.5
Near Total > 90%	N	9
	Percent	10.5
Failure Location		
L+D	N	1
	Percent	1.2
LOCAL	N	3
	Percent	3.5
SPINE	N	3
	Percent	3.5
SUPRATENTORIAL	N	6
	Percent	7.0