

Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma

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ABSTRACT

Purpose

To determine the event-free survival (EFS) and overall survival of children with average-risk medulloblastoma and treated with reduced-dose craniospinal radiotherapy (CSRT) and one of two postradiotherapy chemotherapies.

Methods

Four hundred twenty-one patients between 3 years and 21 years of age with nondisseminated medulloblastoma (MB) were prospectively randomly assigned to treatment with 23.4 Gy of CSRT, 55.8 Gy of posterior fossa RT, plus one of two adjuvant chemotherapy regimens: lomustine (CCNU), cisplatin, and vincristine; or cyclophosphamide, cisplatin, and vincristine.

Results

Forty-two of 421 patients enrolled were excluded from analysis. Sixty-six of the remaining 379 patients had incompletely assessable postoperative studies. Five-year EFS and survival for the cohort of 379 patients was $81\% \pm 2.1\%$ and $86\% \pm 9\%$, respectively (median follow-up over 5 years). EFS was unaffected by sex, race, age, treatment regimen, brainstem involvement, or excessive anaplasia. EFS was detrimentally affected by neuroradiographic unassessability. Patients with areas of frank dissemination had a 5-year EFS of $36\% \pm 15\%$. Sixty-seven percent of progressions had some component of dissemination. There were seven second malignancies. Infections occurred more frequently on the cyclophosphamide arm and electrolyte abnormalities were more common on the CCNU regimen.

Conclusion

This study discloses an encouraging EFS rate for children with nondisseminated MB treated with reduced-dose craniospinal radiation and chemotherapy. Additional, careful, step-wise reductions in CSRT in adequately staged patients may be possible.

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INTRODUCTION

Medulloblastoma, an embryonal tumor of the cerebellum, is the most common brain malignancy occurring in children, comprising 40% of all childhood posterior fossa tumors.¹ Children older than 3 years of age at diagnosis with totally or near totally resected, nondisseminated disease (average risk) have a predicted 5-year progression-free survival of 50% to 65% after 36 Gy of craniospinal radiotherapy (CSRT), supplemented with 18 Gy to 20 Gy of radiotherapy to the posterior fossa.^{2,3} Higher survival rates for children with average-risk disease have been obtained with the addition of chemotherapy to radiation therapy.⁴⁻⁶

Children surviving medulloblastoma are at risk for neurologic, cognitive, and endocrinologic se-

quelae, believed to be due, in great part, to cranial irradiation, and there have been attempts to reduce the dose of CSRT for children without apparent disseminated disease.^{3,7,8,9} Treatment with reduced-dose CSRT (23.4 Gy) without chemotherapy has resulted in a higher likelihood of early isolated neuroaxis relapse.² Children who have received prera-diation chemotherapy and reduced-dose CSRT had a significantly poorer event-free survival (EFS) than those treated with immediate postoperative radiotherapy.^{3,10} However, 80% 5-year survival rates, after treatment with reduced-dose radiotherapy and chemotherapy during and after radiotherapy, have been reported.¹¹

A variety of different chemotherapeutic agents have been utilized either before or after radiotherapy,

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and encouraging results have been obtained with the use of vincristine during radiotherapy followed by cycles of lomustine (CCNU), cisplatin, and vincristine.^{5,6,11} Data supporting the activity of CCNU as an active agent in children with medulloblastoma are relatively scant^{4,5} and in xenograft models and phase II clinical trials, cyclophosphamide has been found to be an active agent.^{12,13} This study was undertaken to determine if a postradiotherapy cyclophosphamide arm would increase the rate of progression-free survival, compared with a CCNU-containing regimen, for children with average-risk medulloblastoma, and to determine the EFS and overall survival and pattern of relapse of children treated with reduced-dose (23.4 Gy) craniospinal radiation therapy.

METHODS

Eligibility

Patients with a histologically confirmed medulloblastoma, between the ages of 3 years and 21 years at the time of diagnosis, were eligible for study. Patients were to have no evidence of disseminated disease on magnetic resonance imaging of the entire brain and spine performed pre- or postoperatively or on cytologic examination of lumbar CSF, performed between 5 days after surgery and the time of radiation. Ventricular CSF could be substituted in only rare instances when lumbar puncture was medically contraindicated. Patients were to have less than 1.5cm² of residual tumor on postoperative neuroimaging performed within 21 days, preferably within 72 hours, of surgery. Patients with brainstem involvement were eligible. Patients were not allowed to have received any previous radiotherapy or chemotherapy, other than corticosteroids, and treatment must have been begun within 31 days of definitive surgery. All institutions participating in the study had received approval from their institutional review boards and age-appropriate informed consent/assent was obtained by each patient/parent/guardian.

Radiotherapy

A dose of 23.40 Gy of craniospinal radiation therapy with a posterior fossa boost of 32.4 Gy (total dose 55.8 Gy) was prescribed in fractions of 18 Gy per day, 5 days per week. Treatment for the craniospinal axis was not to exceed 20 days and the entire treatment was to be completed within 51 days. The whole-brain treatment volume extended to the entire frontal lobe and cribiform plate region. The spinal treatment volume extended laterally to cover the recesses of the entire vertebral bodies with at least a 1 cm margin at either side and inferiorly 1 to 2 cm below the termination of the thecal sac. The boost volume included the entire posterior fossa with a 1 cm margin around the tentorium. Initially, the boost radiotherapy was delivered by parallel opposing fields, but later in the study conformal radiation therapy techniques were allowed.

Chemotherapy

After surgery, eligible patients were randomized to receive eight cycles of either regimen A or regimen B of chemotherapy, as per Table 1, beginning 6 weeks after CSRT. Patients on both regimens were treated with weekly vincristine during radiotherapy (1.5 mg/m², maximum 2.0 mg; maximum of eight doses).

For grade 3 or grade 4 vincristine neurotoxicity, the vincristine was to be held for one dose and restarted at full dosage when symptoms resolved. If symptoms recurred, a reduction in dose of vincristine was allowed. For those on regimen A, if the absolute neutrophil count was below 750 and/or the platelet count of less than 75,000, the cycle of chemotherapy would be delayed. For patients on regimen B, each cycle of chemotherapy had to begin when the absolute neutrophil count was greater than 1,000, with platelets greater than 100,000.

Patients were not to receive cisplatin if creatinine clearances was less than 50% of baseline value. If the creatinine clearance was less than 75% of baseline value, then the cisplatin was reduced by 50%. Audiograms were required before each cycle of chemotherapy. For a decrease in auditory acuity of greater

Table 1. Chemotherapy Regimens

Regimen	Drug	Dosage
A		
Day 0	CCNU	75 mg/m ² by mouth
Day 1	CDDP	75 mg/m ² intravenously
Day 1, 7, 14	VCR	1.5 mg/m ² ; max 2 mg intravenous bolus, maximum of eight doses
B		
Day 0	CDDP	75 mg/m ² intravenously
Day 1, 7, 14	VCR	1.5 mg/m ² ; max 2 mg, intravenous bolus
Day 21, 22	Cyclo	1,000 mg/m ² intravenously over 60 min daily

Abbreviations: CCNU, lomustine; CDDP, cisplatin; VCR, vincristine; max, maximum; Cyclo, cyclophosphamide; min, minute.

than 30 decibels at 4,000 hz to 8,000 hz, a 50% in cisplatin was mandated. For a greater than 20 decibels loss at 500 hz to 3,000 hz, at 50% reduction in cisplatin dosage was made. For grade 4 ototoxicity, cisplatin was held and not restarted unless follow-up audiograms returned to at least no more than grade 2 ototoxicity.

Staging Review

Preoperative and postoperative magnetic resonance imaging scans were centrally reviewed on 409 (97%) of 421 of studies by two radiologists (G.V. and J.L.) for evaluation of extent of disease and amount of postoperative residual disease. If, on central review, their studies were incomplete or thought to be unassessable because of movement or other artifacts, patients were considered incompletely assessable, but remained eligible for analysis. Eligibility was based on institutional review except when central review revealed unequivocal evidence of dissemination or excess residual disease, in which case for analysis the patient was considered ineligible.

Pathology Review

Central pathologic review was performed on 358 (85%) of 421 of specimens by one of two neuropathologists (L.R.-A. and P.C.B.). In addition to determination of tumor type, the pathologists were asked to evaluate the tumors for evidence of excessive focal or diffuse anaplasia (no formal grading system was employed).

Statistical Considerations

Patients were randomly assigned to one of the two experimental regimens at the time of study enrollment, stratified by age and brainstem involvement. The primary end point for analysis was time to a treatment failure event (EFS) measured from the time of study enrollment. An event was defined as the first occurrence of death from any cause, relapse, progressive disease, or development of a second malignancy. The secondary end point was time to death from any cause, from which actuarial survival probability was computed. The original design called for 240 to 300 randomly assigned patients enrolled over 4 years. The stated power of the two-sided logrank test based on this, an assumed baseline EFS of 85% at 1 year and 70% long-term EFS (cure rate), and a minimum of 2 years of follow-up on the last patient, was 79% power for an improvement in long-term EFS from 70% to 85% (increase by 15%). As noted, however, the rate of patient enrollment was higher than originally anticipated. For the primary comparison, 379 patients were enrolled over 4 years, and analysis was performed with a minimum of 3 years follow-up. With the same baseline EFS assumptions above, this would correspond to 80% power to detect an increase in long-term EFS from 70% to 83%, or a 13% improvement.^{14,15,16} All analyses followed the intent-to-treat philosophy, in that patients were censored only for reasons of follow-up. Interim results were reviewed annually by an independent data and safety monitoring committee.

Nonparametric EFS and survival curves were computed using the product-limit (Kaplan-Meier) estimates, with SE via the Greenwood formula.¹⁵ Follow-up probabilities were also estimated using the product-limit estimate by censoring patients experiencing treatment failure events. Cumulative toxicity rates are also computed actuarially.

RESULTS

Between December 1996 and December 2000, 421 patients were enrolled on this study. Forty-two of these patients were excluded from the analysis after central review (Table 2). The remaining 379 patients include 66 patients who, on central review, had no clear evidence of excess residual or metastatic disease, but whose studies could not be fully evaluated because of poor quality or incompleteness of submission. Patient characteristics are in Table 3. Median follow-up (last patient enrolled 57 months ago) is just more than 5 years, with all patients having been observed at least 3 years, 81% at least 4 years, and 57% at least 5 years.

Treatment Toxicity

Table 4 shows the cumulative rate of key toxicities over the entire course of therapy. Virtually all patients experienced grade 3 or 4 hematologic toxicity sometime during therapy. Grade 4 hematologic toxicity and infections occurred significantly more frequently in patients treated with regimen B. Electrolyte toxicity and poor performance score occurred more frequently in patients treated with regimen A.

Treatment Failures

Seventy-three patients have experienced a treatment failure event, as defined by their treating institution, and 54 have died. On central neuroradiographic analysis, the reviewers believed that the area considered by the institution to demonstrate tumor progression was equivocal in two, and in five others, represented gliosis (two patients), cerebellar treatment-related demyelination (one patient), lumbar nerve root enhancement (one patient), or a vein on dorsum of the conus (one patient). However, for analysis, all these patients are considered treatment failures. Three of these patients remain alive, after various forms of retreatment, for longer than 5 years after relapse, and four patients died of progressive disease. One patient suffered an aortic hemorrhage during radiotherapy (of unclear etiology), and another succumbed due to extensive brainstem necrosis. Seven patients experienced second malignant neoplasms as a first event, an average of 59 months from study enrollment and three patients died. Details are summarized in Table 5. The remaining 64 patients experienced tumor progression or relapse, and 45 patients died. Sites of progression/recurrence are summarized in Table 6.

Overall Outcome and Treatment Effect

Figure 1 shows EFS and survival for the entire patient cohort as determined by institutional review. Five-year EFS and survival

Reason for Exclusion	No. of Patients
Unequivocal residual disease, greater than 1.5 cm ²	15
Metastatic disease	15
Ineligible pathology	4
Glioma	1
Undetermined	1
Incomplete staging	4
Excessive delay in initiation of treatment	1
Inadequate informed consent	1
No follow-up	2

Characteristic	No.	%
Sex		
Male	223	59
Female	156	41
Ethnicity		
White	299	80
Hispanic	36	10
Black	20	5
Other	19	5
Age, years		
3-4	65	17
5-9	193	51
10-14	96	25
15-19	25	7
Randomized regimen		
A	193	51
B	186	49
Brain stem involvement		
No	326	86
Yes	53	14
Anaplasia		
None (nonexcessive)	279	85
Diffuse	30	9
Focal	18	6
Not specified	1	0
Unknown	51	—
Assessability		
Eligible, fully assessable	313	83
Eligible, not fully assessable	66	17
Not eligible, excess residual	15	—
Not eligible, disseminated	15	—
Not reviewed	12	—
RT quality review		
RT per protocol	279	79
Volume too small (either fossa or craniospinal axis)	74	21
Not done/not assessable	26	—

Abbreviation: RT, radiotherapy.

probabilities are $81\% \pm 2.1\%$ and $86\% \pm 1.9\%$, respectively. Figures 2 and 3 show EFS and survival, respectively, by randomized treatment assignment. Five-year EFS is $82\% \pm 2.8\%$ and $80\% \pm 3.1\%$ for regimens A and B, respectively. Five-year survival is $87\% \pm 2.6\%$ and $85\% \pm 2.8\%$.

Prognostic Factors

Table 6 summarizes 3- and 5- year EFS within patient categories defined by sex, race, age, brainstem involvement, and whether the tumor displayed features of excessive anaplasia. None of these factors was a statistically significant predictor of EFS. Patients whose tumors displayed features of excessive anaplasia had nominally worse outcome at 5 years: EFS $83\% \pm 2.3\%$ versus $73\% \pm 6.4\%$ ($P = .087$); and significantly worse survival: $89\% \pm 1.9\%$ versus $75\% \pm 6.4\%$ ($P = .005$). No difference in EFS could be detected depending on whether severe anaplasia was focal or diffuse ($P = .89$; Fig 4), nor did the pattern of failure or relapse differ in patients with anaplastic versus nonanaplastic tumors.

Table 4. Cumulative Toxicity Rate

Toxicity	Grade 3 or 4 Regimen A/B		Grade 4 Regimen A/B		
	%	P	%	P	
	Hematologic	97/98		82/90	
Hepatic	12/11		1.7/2.2		
Renal	9.0/5.0		1.1/0.0		
Pulmonary	3.4/2.2		1.6/1.6		
Nervous system	51/46		5.4/3.8		
Hearing	28/23		5.8/6.7		
Electrolytes	6.2/12	< .10	1.7/3.9		
Infection	18/30	< .01	1.6/6.9	< .05	
Performance	21/14	< .10	4.9/4.8		

Comparison Based on Assessability

A comparison of EFS in the 313 fully assessable patients, the 66 patients who were incompletely assessable, and the 15 patients who were considered ineligible because of unequivocal excess residual or disseminated disease on review is shown in Figure 5 and Table 7. Five-year EFS was 83% ± 2.2% versus 73% ± 5.8% versus 75% ± 13% versus 36% ± 15% in these four groups, respectively (logrank $P < .005$). There was no detectable difference in the pattern of relapse between these patient groups.

DISCUSSION

The results of this study, the largest prospective randomized trial ever performed for children with medulloblastoma, discloses an encouraging 81% ± 2% 5-year EFS rate for children older than 3 years of age with nondisseminated disease, which is essentially identical to the EFS obtained in previous prospective studies which utilized either 36 Gy or 24 Gy of CSRT and regimen A used in the study.^{5,6,11} The EFS rate compares favorably with results obtained after treatment with radiotherapy alone, including a contemporary prospective trial which found a 64.8% EFS rate for nondisseminated patients treated with 36 Gy of CSRT and supports the use of chemotherapy for all children with medulloblastoma.^{3,17} The results of our trial also are as good, if not better, than the highest reported survival rates in studies using higher doses of CSRT with more intensive chemotherapy regimens.^{18,19} It is conceivable that as imaging techniques have improved, more patients who are now considered average risk may

Table 5. Second Malignant Neoplasms

Diagnosis (site)	Month	Regimen
MDS	76	A
Pilocytic astrocytoma	77	A
T-ALL	38	A
Malignant glioma (cerebellar)	62	B
Basal cell carcinoma	56	A
Glioblastoma (temporal)	63	B
Glioblastoma (cerebellar)	44	B

Abbreviations: MDS, myelodysplastic syndrome; T-ALL, T-cell acute lymphoblastic leukemia.

Table 6. Sites of Recurrence/Progression

Site of Recurrence/Progression	No. of Patients
PF alone	20
PF + brain/spine met	16
Brain/spine met alone	23
Brain/spine + extraneural met	1
Extraneural alone	1
Unknown	1

Abbreviations: PF, posterior fossa; met, metastatic.

have been classified as poor risk in past studies, possibly artificially improving comparative outcomes. The incorporation of molecular parameters into stratification may make comparisons to older studies difficult, however, molecularly based stratification might also identify patients who will be amenable to treatment with even less aggressive therapy.²⁰⁻³¹

The pattern of relapse seen in this series raises the issue of whether reduced (23.4 Gy) craniospinal radiotherapy is adequate to prevent distant disease relapse. Posterior fossa relapse alone occurred in 20 (32%) of 63 assessable patients, with 43 patients having either disseminated relapse alone (40%) or posterior fossa and distant relapse (25%). In a study which utilized 36 Gy of CSRT therapy, isolated posterior fossa relapse occurred in 11 (34.4%) of 32 patients, essentially identical to that seen in our study.¹⁷ It is likely that a subset of initially nondisseminated medulloblastomas are likely to relapse outside the primary tumor site, independent of the dose of CSRT, due to not fully defined biologic predispositions.²⁵

The presence of anaplastic histologic features has been found in retrospective reviews of patients, treated in a variety of ways, to be related to poorer outcome.³² In our study, excessive anaplasia, be it diffuse or focal, was identified in 49 patients (15%) and was related to poorer overall survival. Parameters such as marked nuclear atypia, cytological pleomorphism, numerous mitosis, and apoptotic bodies are used to determine the degree of anaplasia. Some degree of anaplasia occurs in the majority of medulloblastomas and it was left to the subjective impressions of the two senior review neuropathologists if anaplasia was excessive.³² Other factors, such as sex, race, age at diagnosis, or brainstem involvement were not predictive of EFS. In a recent

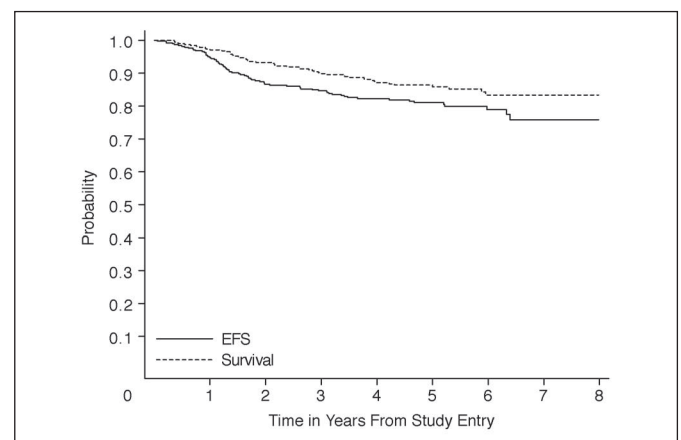


Fig 1. Event-free survival (EFS) and survival from study entry.

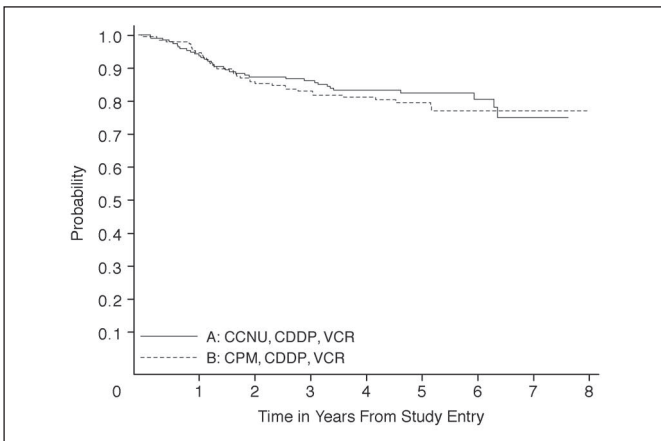


Fig 2. Event-free survival from study entry by treatment regimen. CCNU, lomustine; CDDP, cisplatin; VCR, vincristine; CPM, cyclophosphamide.

international study, overall survival and EFS were detrimentally affected if radiotherapy was completed in longer than 50 days.¹⁷ In our study, unlike the international study which treated patients with preirradiation chemotherapy, none had prolongation or delays in delivering radiotherapy. The major deviations in our series were due to targeting deviations and there was no significant impact on EFS or survival.

As patients in this study received only chemotherapy during and after radiotherapy, no direct conclusions can be drawn concerning the relative merits of pre- versus postradiotherapy chemotherapy. In randomized studies addressing this issue, preirradiation chemotherapy has been associated with poorer disease control than chemotherapy after radiotherapy, especially when the dose of radiotherapy was reduced.^{2,10,18} A French Society of Pediatric Oncology study, treating a cohort of patients similar to ours with preirradiation chemotherapy and 25 Gy of CSRT after surgery, found a 5-year disease-free survival rate of approximately 65%, which seems inferior to our results.³³

Our study demonstrates that both the CCNU and cyclophosphamide treatment arms result in similar progression-free and overall survival and that both arms have significant, but tolerable toxicity. In the newly-opened Children's Oncology Group study for average-risk

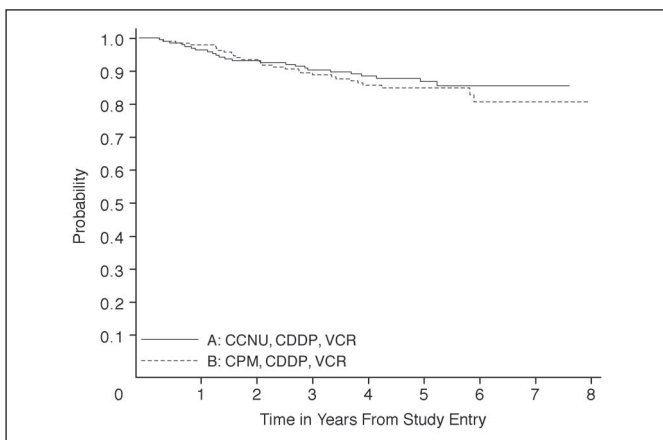


Fig 3. Survival from study entry by treatment. CCNU, lomustine; CDDP, cisplatin; VCR, vincristine; CPM, cyclophosphamide.

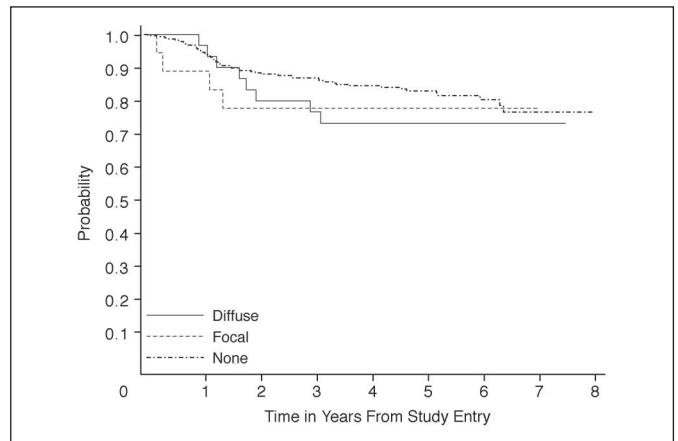


Fig 4. Event-free survival by anaplasia.

medulloblastoma, both drugs were incorporated. A major issue remains audiologic toxicity, thought predominantly due to cisplatin. Grade 3 or 4 toxicity was seen in nearly one quarter of the cohort, suggesting that stricter stopping rules needs to be utilized for cisplatin-associated hearing loss or alternatively, the cumulative dose of cisplatin be carefully reduced.

A cautionary finding in this study was the results of central neuroradiographic review. Thirty of 409 reviewed patients had what was considered unequivocal evidence of residual or metastatic disease by the central reviewers and 66 had studies that were considered incomplete or of poor quality. Five-year EFS was poorer in patients with incompletely assessable studies, as compared with those with centrally reviewed adequate studies and was dismal, as could be expected, for those patients who, in retrospect, were inappropriately assigned to the study with disseminated disease. This shows the critical importance of adequate neuroimaging and interpretation, so as not to put patients who have disseminated medulloblastoma (see Fig 5) at undue risk. Another concerning finding was the disparity in seven patients between central review and institutional review in the determination of disease progression. Nonspecific nerve root enhancement, postsurgery gliosis, and post-treatment tissue damage can be difficult to separate from tumor recurrence. The presence of secondary tumors in seven patients,

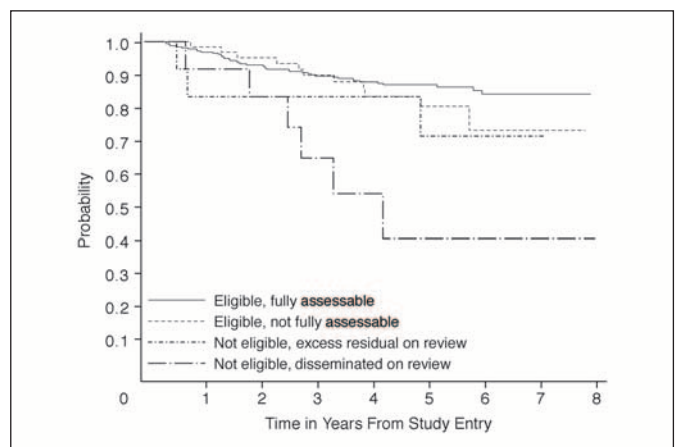


Fig 5. Comparison of event-free survival based on assessability status.

Table 7. EFS by Patient and Tumor Characteristics

Characteristic	3-Year EFS		5-Year EFS		P
	%	SE	%	SE	
Sex					.36
Male	83	2.5	79	2.8	
Female	87	2.8	84	3.1	
Ethnicity					.90
White	83	2.2	81	2.4	
Hispanic	92	4.6	86	6.0	
Black	79	9.4	73	10	
Other	88	6.8	79	8.5	
Age, years					.97
3-4	84	4.6	80	5.2	
5-9	86	2.5	82	2.9	
10-14	81	4.1	80	4.2	
15-19	88	6.6	83	7.8	
Randomized regimen					.40*
A	86	2.5	82	2.8	
B	83	2.8	80	3.1	
Excessive anaplasia					.15†
No	87	2.0	83	2.3	
Yes	75	6.2	73	6.4	
Diffuse‡	77	7.7	73	8.1	.86§
Focal‡	78	9.8	78	9.8	
Brain stem involvement					.71
No	87	4.7	77	6.1	
Yes	84	2.0	82	2.2	
Assessability¶					< .005
Eligible, fully assessable	86	2.0	83	2.2	
Eligible, incompletely assessable	77	5.5	73	5.8	
Not eligible, excess residual	83	11	75	13	
Not eligible, disseminated	48	15	36	15	
RT quality					.86
RT per protocol	83	2.3	81	2.4	
Volume deviation	91	3.4	82	5.0	
Not done/not assessable	83	7.9	83	7.9	

Abbreviations: EFS, event-free survival; RT, radiotherapy.
 *Stratified logrank test.
 †Yes versus no.
 ‡Excludes one patient with indeterminate anaplasia.
 §Diffuse versus focal.
 ¶Includes 30 additional patients ruled ineligible due to dissemination or excess residual on review.

including three with malignant gliomas, with still a relatively short period of follow-up, is of concern.

The neurocognitive, endocrinologic, and pulmonary outcome of patients treated on this study remains in analysis. In an ancillary study evaluating the acute postoperative neurologic status of patients entered on this trial, nearly one quarter of children were found to have postoperative delayed onset mutism, hypotonia, cerebellar deficits, supranuclear cranial nerve deficits, and extreme irritability and/or emotional lability (posterior fossa mutism syndrome).^{34,35} Approximately one half of affected patients had residual deficits 1 year later.³⁵ This must be taken into account when assessing the long-term sequelae of treatment. From previous ret-

rospective and prospective studies, it is likely that even after 23.4 Gy of craniopsinal irradiation therapy that children, especially those between 3 years and 7 years of age at diagnosis, will suffer significant learning and other associated cognitive complications.⁸ The results of our study raises the possibility that the dose of CSRT can be reduced even further, especially in meticulously staged patients without evidence of disseminated disease. This is the approach being utilized in the follow-up Children's Oncology Group average-risk medulloblastoma study, randomly assigning children between 18 Gy and 23.4 Gy of CSRT. The EFS rate should be the basis of comparisons for future studies evaluating alternative means to treat this patient population.

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