Long Term Survivors of Childhood Brain Stem Gliomas Treated with Hyperfractionated Radiotherapy

Clinical Characteristics and Treatment Related Toxicities

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BACKGROUND. Over the past decade, the principal focus of research in pediatric brain stem gliomas has been on the use of hyperfractionated radiotherapy (HRT). The purpose of this study was to evaluate the clinical characteristics and treatment related toxicities of long term survivors of HRT treatment.

METHODS. Of the 130 children with brain stem tumors treated with escalating doses of HRT on Pediatric Oncology Group (POG) #8495, there are only 9 long term survivors. Prospectively collected data, including flow sheets and all pretreatment and follow-up radiologic studies, were reviewed for these patients. Additional information was requested from the treating institutions with regard to sequelae of treatment.

RESULTS. Clinical characteristics (including age, sex, duration of symptoms, and presenting signs) for the nine surviving patients were not different from the total population of patients treated on POG #8495. Pretreatment imaging, however, revealed that only four of the nine patients had typical diffuse intrinsic pontine lesions and, conversely, that at least three of the nine patients had lesions that would now be considered relatively favorable. Complete information regarding treatment related toxicity was available for eight patients, only one of whom is without sequelae. Seven have schooling difficulties, two have a seizure disorder, five have hearing loss, and two have required growth hormone replacement. Follow-up imaging findings were striking in four of the eight patients because of white matter changes consistent with leukoencephalopathy (two patients), diffuse microhemorrhages (one patient), and dystrophic calcification (one patient) in the radiation field.

CONCLUSIONS. The high frequency of treatment related sequelae in long term survivors of HRT suggests a need for caution in the use of HRT, particularly in patients who have brain stem tumors with a more favorable prognosis. ***Cancer* 1996; 77:555–62.** © *1996 American Cancer Society.*

KEYWORDS: brain stem tumors, hyperfractionated radiotherapy, radiotherapy, treatment.

In 1984, the Pediatric Oncology Group (POG) began accrual to a Phase I/II study designed to test the efficacy and toxicity of sequentially escalated doses of hyperfractionated (twice daily) radiotherapy (HRT) in children with brain stem tumors.

The eligibility criteria for POG #8495 have been described in detail elsewhere;[1] briefly, the intent was to select out, on the basis of clinical and radiologic findings, a poor risk group of patients for study. The results of treatment of the 34 evaluable patients treated between September 1984 and January 1986 at the first dose level (66 Gy given in 60 twice daily fractions of 1.1 Gy over 6 weeks), of the 57 patients treated between May 1986 and February 1988 at the second dose level (70.2 Gy given in 60

twice daily fractions of 1.17 Gy over 6 weeks), and of the 39 evaluable patients treated between May 1989 and June 1990 at the third dose level (75.6 Gy given in 60 twice daily fractions of 1.26 Gy over 6 weeks) have been reported elsewhere.[1-3] Although median time to disease progression and survival at one year were quite similar at the three dose levels, there was a trend toward improved survival at the second dose level (70.2 Gy) and POG has gone on to test hyperfractionated radiotherapy at this dose level against conventional radiotherapy to 54 Gy in an ongoing prospective, randomized Phase III trial.

There are only 9 long term survivors out of a total of 130 evaluable patients treated with HRT on POG #8495. Careful review of the pretreatment clinical and radiologic findings, as well as posttreatment magnetic resonance imaging (MRI) findings, proved to be of considerable interest and are reported here because of the implications of the findings, most especially with regard to children with relatively favorable tumors for whom the risks of treatment with hyperfractionated radiotherapy as given in the POG study may be considered unacceptable.

PATIENTS AND METHODS

Prospectively collected data, including flow sheets and all pretreatment and follow-up radiologic studies, for the surviving patients were reviewed. Letters were sent to the treating radiation oncologists and/or other physicians involved in the care of the children requesting additional information with regard to the status of the patients at their most recent follow-up visit. Specific information was requested with regard to sequelae of treatment, including any neurologic deficits, hearing loss, and endocrine abnormalities; academic performance was evaluated.

Pretreatment clinical and imaging findings were reviewed for all nine patients. Recent follow-up information and detailed evaluation of sequelae of treatment, as well as follow-up imaging studies, were available for eight of the nine children. These data are presented in Table I.

RESULTS

There were 5 females and 4 males with ages at diagnosis ranging from 5 to 15 years (median, 8 years). The duration of symptoms prior to diagnosis had ranged from two weeks to one year (median, two months). Symptoms included *headache* and emesis in four of the nine patients. Neurologic abnormalities at diagnosis included cranial nerve palsies in seven patients, ataxia in six patients, and long tract signs in four patients; four of the nine patients had presented with all three types of deficit.

Pretreatment imaging revealed typical diffuse intrinsic pontine lesions in only four of the nine patients. Three additional patients had intrinsic pontine lesions but one was clearly focal, another was a cystic tumor with a small mural nodule, and the third had a large intrinsic but well marginated lesion that was cystic with mural enhancement after administration of contrast material. One patient had a large intrinsic lesion confined to the midbrain. One had a dorsally exophytic tumor arising from the medulla. Hydrocephalus was present at diagnosis in two patients; in one, the patient with the focal lesion involving the pons, it had been present since birth. The second, a patient with a typical diffuse intrinsic pontine lesion with extension to the midbrain and medulla, had been noted to be clumsy and inattentive for several years but actually presented with a two-month history of cranial nerve paresis.

Five of the nine patients underwent surgery. The patient with the dorsally exophytic tumor underwent complete resection of her tumor and the patient with the well marginated cystic intrinsic pontine lesion underwent what was described as subtotal resection. Biopsy only was performed in three patients. Tissue adequate for diagnosis was obtained in all five patients. Central review of pathologic material confirmed a diagnosis of astrocytoma in three patients and anaplastic astrocytoma in two patients. Seven of the nine patients received radiotherapy at the 70.2 Gy dose level. One patient received 66 Gy and one patient 75.6 Gy. The duration of follow-up, starting from the date of initiation of treatment with radiotherapy, ranged from 64 to 109 months (median, 91 months).

Only one of the eight patients for whom detailed recent follow-up was available has no sequelae of treatment. The patient with the dorsal exophytic tumor who was treated with complete resection followed by HRT to a dose of 66 Gy remains completely well; her academic performance has always been above average. Seven of the eight patients have schooling difficulties. However, in six of the seven children the difficulties are minor and only one of the children is in a special education program. Two patients have a seizure disorder that started 66 and 87 months, respectively, after treatment; in both, the seizures are well controlled with medication. Five children, including one who has had repeated ear infections, suffered hearing loss; two children require amplification. Two patients required growth hormone replacement.

Follow-up imaging findings are striking. Of the 8 studies performed at a median of 74 months posttreatment, 2 are normal and 2 show changes confined to the primary site in the brain stem. Four of the eight patients have impressive changes outside the brain stem but within the radiation field. These four patients are described in detail below.

Two children have white matter changes compatible with leukoencephalopathy. One of the two children, a patient with a diffuse intrinsic lesion involving the midbrain and pons who was treated with HRT to a dose of 70.2 Gy, developed a number of problems in the follow-up period, including mild schooling difficulties, decreased hearing that does not require amplification, and growth hormone deficiency. At 87 months posttreatment,

TABLE 1
Clinical Characteristics, Treatment, and Outcome in Nine Long Term Survivors of HRT on POG #8495

					Neuro findings			Imaging findings			Treatment			FU	Late effects				
Sex	Age	Duration of symptoms	H/A, Emesis	Other	Ataxia	LT	CrN	Loc	Type	Hydro	S	RT dose	Start	(mos)	School	Endo	Hearing	Other	Imaging
F	11 yrs	1 yr	+		+			Md	D Exo	N	CR (Fib)	66 Gy	11/85	109					None
F	8 yrs	6 wks			+	+	+	P	Foc/cystic	N	Bx (Astro)	70.2 Gy	5/86	89	minor		+	Ear inf.	None
M	12 yrs	2 wks	+		+	+	+	P	Foc	Y since birth	–	70.2 Gy	8/86	99	minor		+	Seizures	Microhemorrhages
F	5 yrs	6 mos			+	+	+	Mb P	DI with large ventral exo	N	Bx (Astro)	70.2 Gy	8/86	91	minor	GH	+	Seizures	Leucoencephalopathy
F	15 yrs	6 wks					+	Mb P	DI	N	Bx (AA)	70.2 Gy	10/86	96	N/A	N/A	N/A	N/A	N/A
F	12 yrs	2 wks	+					Mb P	Well-marginated, cystic, wall enhancement	N	ST (AA)	70.2 Gy	1/87	78	minor				Encephalomalacia in P
M	7 yrs	2 mos		inattentive clumsy "several yrs"			+	Mb P Md	DI	Y	–	70.2 Gy	7/87	92	minor	GH	+		Dystrophic Ca
M	7 yrs	2 mos			+	+	+	Mb P Md Cereb.	DI	N	–	70.2 Gy	7/87	86	special ed.				Dystrophic Ca in P
M	6 yrs	6 mos	+		+		+	P Md	DI	N	–	75.6 Gy	10/89	64	minor		+		Leucoencephalopathy

HRT: hyperfractionated radiotherapy; POG: Pediatric Oncology Group; H/A: headache; FU: follow-up; LT: long tract; CrN: cranial nerve; Loc: location; Hydro: hydrocephalus; S: surgery; RT: radiotherapy; Endo: endocrine abnormalities; F: female; M: male; Mb: midbrain; P: pons; Md: medulla; Cereb: cerebellum; D Exo: dorsal exophytic; Foc: focal; DI: diffuse intrinsic; N: no; Y: yes; CR: complete resection; Fib: fibrillary; Bx: biopsy; Astro: astrocytoma; AA: anaplastic astrocytoma; ST: subtotal resection; N/A: not available; GH: growth hormone deficiency; Ca: calcification.

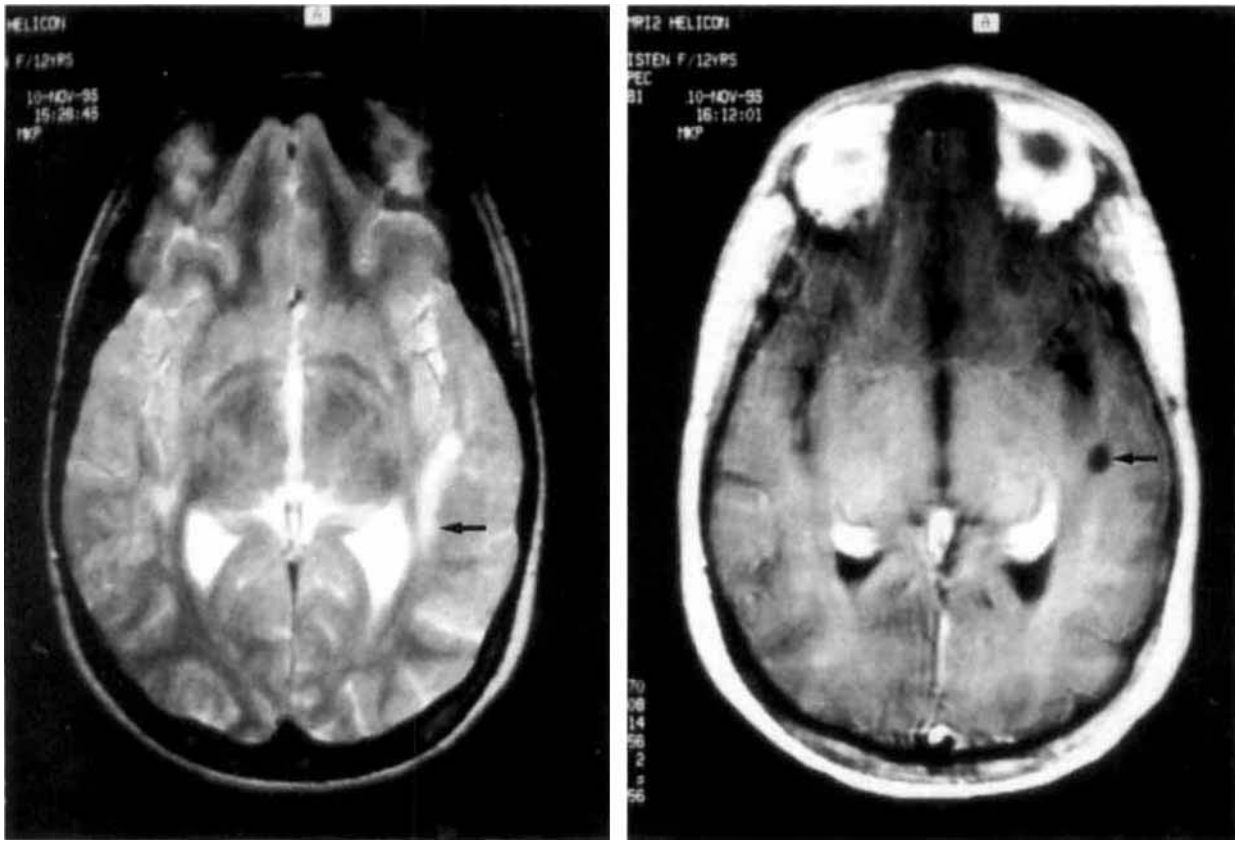

FIGURE 1. (Left) Axial T2-weighted magnetic resonance image obtained at 87 months posttreatment shows areas of hyperintensity in periventricular white matter consistent with postradiation leukoencephalopathy (arrow). (Right) Postgadolinium axial T1-weighted image shows a 7-mm nonenhancing cyst in the left temporal lobe inside an area of leukoencephalopathy (arrow).

she developed temporal lobe seizures that are well controlled with carbamazepine (Tegretol, Ciba-Geigy, Summit, NJ). Her MRI scan at 81 months showed multiple areas of hyperintensity in the white matter adjacent to the occipital horns. There is also a small cyst in the medial aspect of the left temporal lobe that may represent an area of radionecrosis (Fig. 1). The second patient, with a diffuse intrinsic lesion involving the pons and medulla, was the only survivor in the cohort of 39 patients treated at the highest dose level (75.6 Gy). His MRI scan at 14 months showed linear and nodular lesions distributed symmetrically in the white matter in the radiation field that were interpreted as metastatic disease (Fig. 2). However, he received no further treatment and remains well, with mild hearing loss and minor schooling difficulties, at 64 months posttreatment.

The third patient, a child with a focal lesion in the pons who was treated with HRT to a dose of 70.2 Gy, has minor schooling difficulties and a hearing deficit that is managed with amplification. At 66 months posttreatment, he developed a seizure disorder for which he is treated with carbamazepine. An MRI scan at 67 months showed evidence of previous hemorrhage in the right temporal lobe within the radiation field (Fig. 3).

The fourth patient, a child with a diffuse intrinsic pontine lesion that extended to the midbrain and medulla, who was treated with HRT to a dose of 70.2 Gy following treatment, developed behavioral problems and schooling difficulties, as well as a hearing deficit requiring amplification and growth hormone deficiency. On computed tomography (CT) scan at 68 months posttreatment, areas of dystrophic calcification are seen in the cerebellar hemispheres and the temporoparietal junctions within the radiation field (Fig. 4).

DISCUSSION

Progress in the management of children with brain stem gliomas over the past decade has resulted from improvements in neuroimaging that, when correlated with the clinical findings, have led to the identification of several distinct subtypes.[4-9] With parallel improvements in neurosurgical techniques, including intraoperative monitoring of the extent of tumor resection by ultrasound and computer reconstruction techniques as well as of evoked

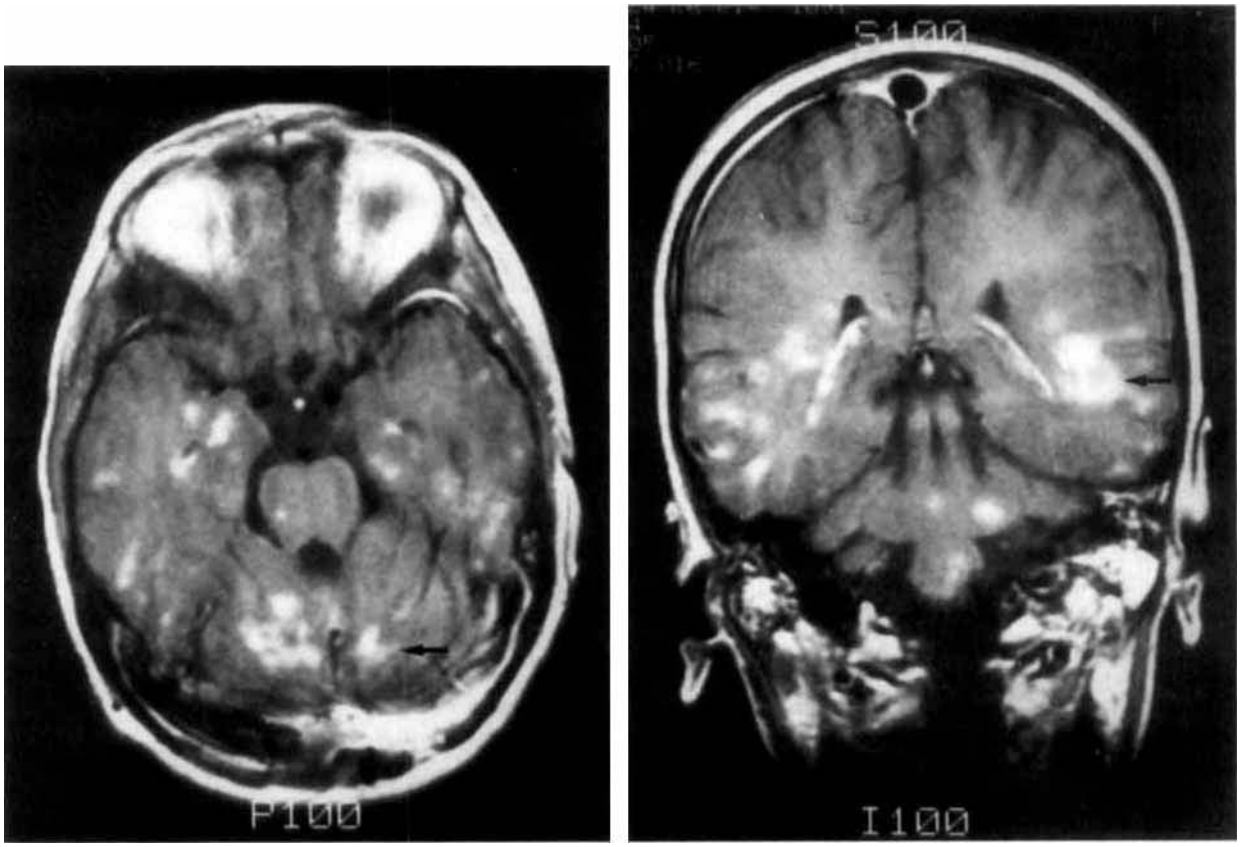

FIGURE 2. (Left) Axial and (Right) coronal postgadolinium T1-weighted images show multiple enhancing linear and nodular lesions in subcortical and periventricular white matter distributed symmetrically in the radiation field (arrows).

potentials, surgery is now considered to be the treatment of choice for tumors that are focal and surgically accessible, for dorsally exophytic tumors, and for tumors arising at the cervicomedullary junction.[7,8,10–12] Adjuvant therapy is usually not necessary and the prognosis for this highly selected group of patients may be excellent.

By contrast, patients with diffuse intrinsic pontine lesions who have traditionally been treated with radiotherapy, often without histologic confirmation of diagnosis, and for whom surgery is not an option, continue to fare poorly. Over the past decade, the principal focus of clinical research for patients with these tumors has been on the use of hyperfractionated radiotherapy.[1–3,13–18] The rationale for hyperfractionated radiotherapy has been described in detail elsewhere.[19] For patients with brain stem tumors, it was hypothesized that the higher total doses of radiation that can be given by using a larger number of smaller radiotherapy dose fractions would result in improved tumor control for a lesser or equivalent risk of injury to the brain. In Phase I/II studies, lower doses of HRT of 64.8 Gy (Childrens Hospital of Philadelphia [CHOP])[13] and 66 Gy (POG)[1] resulted in no unusual toxicity. At moderate doses of 70.2 Gy (POG)[2] and 72 Gy (University of California at San Francisco [UCSF])[14] and the Children's Cancer Group [CCG] pilot[15]), there was a suggestion of increased efficacy. However, results of a subsequent CCG study[17] did not confirm this finding and no further gains in efficacy were seen at the highest dose levels of 75.6 Gy (POG[3]) and 78 Gy (UCSF[16] and CCG[18]). Moreover, at the 75.6 Gy dose level of the POG study, there appeared to be increased acute and subacute toxicity that consisted principally of steroid dependency and intralesional necrosis.[3] The intermediate dose level was therefore considered to be the one that had shown the best therapeutic ratio and the value of HRT at the 70.2 Gy dose level is currently being tested in a Phase III study. Until a therapeutic gain for HRT can be demonstrated, practicalities concerning the use of twice daily radiotherapy in this young patient population, as well as concerns regarding toxicity, dictate that conventional, once daily radiotherapy should remain the standard of care for patients with brain stem tumors.

This is especially the case for patients with what are now considered to be relatively favorable lesions who may do well after surgery alone or other treatments (including conventional radiotherapy) with less risk of morbidity. Although POG #8495 was designed to exclude such patients, it is noteworthy that, in retrospect and based

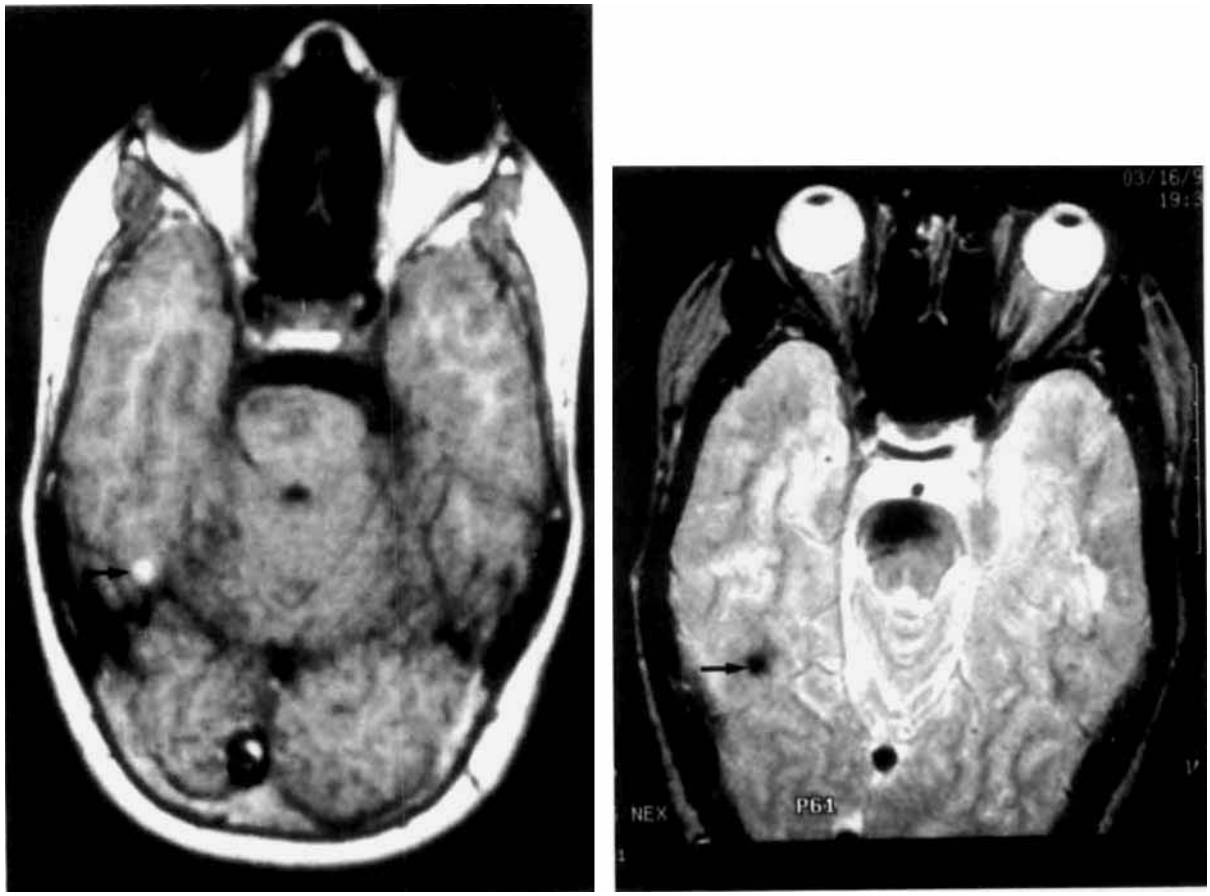

FIGURE 3. (Left) Plain T1-weighted magnetic resonance image obtained at 17 months posttreatment shows a small hyperintense area in the posterior portion of the right temporal lobe consistent with subacute hemorrhage with methemoglobin deposition. (Right) T2-weighted image obtained more than 4 years later, at 67 months posttreatment, shows a hypointense area in the same location, consistent with a previous hemorrhage with hemosiderin deposition.

on current knowledge of brain stem tumors, at least three of the nine long term survivors in fact had tumors that would fit into this category, and, conversely, only four of the nine survivors' tumors had the typical appearance of a diffuse intrinsic pontine tumor. Because the numbers are small, it is difficult to compare the clinical characteristics and presentation of these patients with the whole cohort of patients treated on POG #8495, but the age, sex, median duration of symptoms, and neurologic findings at presentation appear to be similar. However, it is noteworthy that, in retrospect, three of the nine survivors had had symptoms for longer than six months at diagnosis; one had had hydrocephalus since birth, one was said to have been noted to be inattentive and clumsy for several years, and one had complained of headaches for one year.

Detailed review of the small number of survivors of treatment on the POG hyperfractionation study shows a very high frequency of significant sequelae after treatment. Some, such as growth hormone deficiency and hearing loss, are not unexpected, given the treatment technique utilized and clearly it is essential that patients be monitored closely after treatment in order to ensure timely intervention. Others, such as the abnormalities seen on CT and MRI, associated in two patients with a late developing seizure disorder, are of great concern. These findings have not been described by other groups that have tested hyperfractionated radiotherapy in children with brain stem gliomas, but it seems unlikely that our findings will be unique.

This study clearly demonstrates the importance of careful long term follow-up of patients treated with experimental approaches; our observations with regard to long term toxicity in the small number of surviving patients should weigh heavily in therapeutic decision-making, particularly in the management of patients with more favorable lesions.

To what extent it is possible to obviate any or all of the long term sequelae of treatment by attention to details of treatment, such as the energy of the radiation beam, the field arrangement, and the use of customised

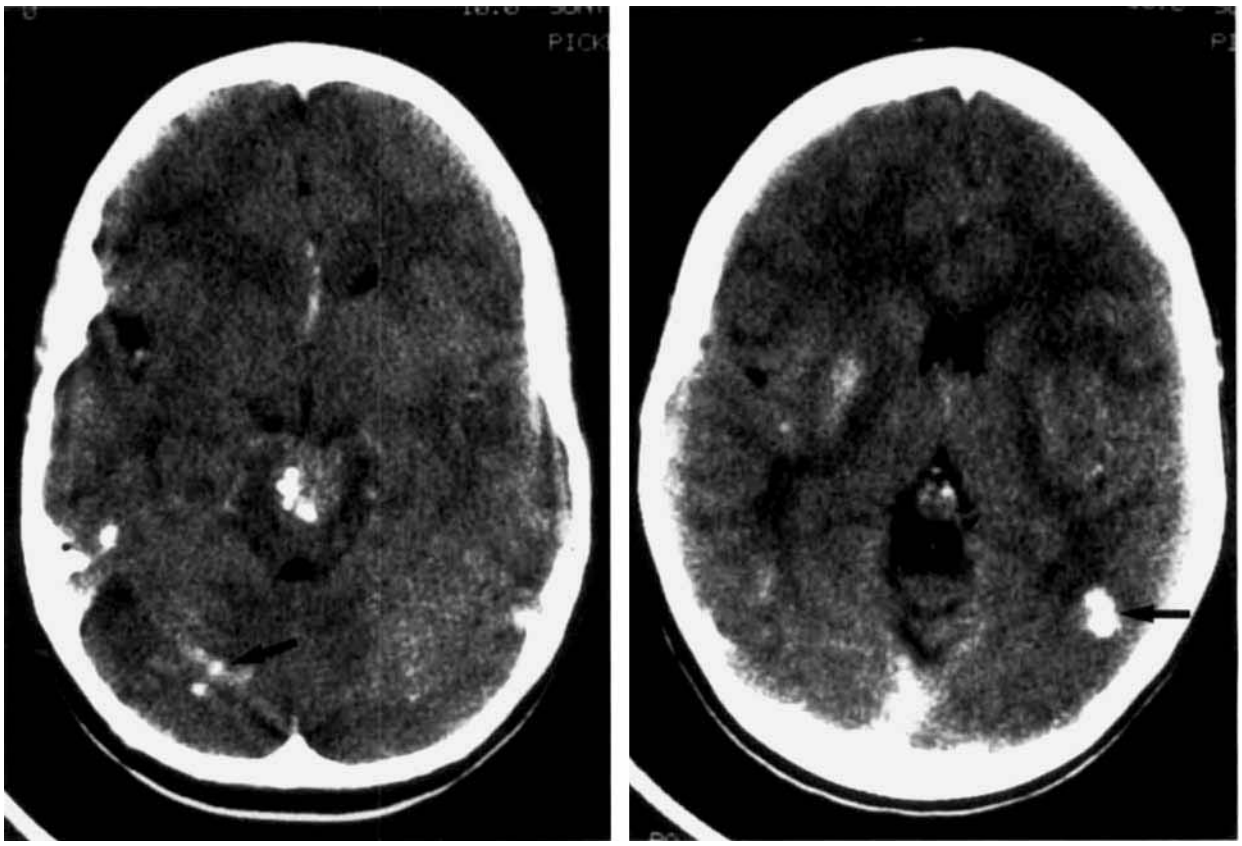

FIGURE 4. (Left and Right) Axial plain computed tomography scan shows calcifications in the pons, right and left cerebellar hemispheres, and temporoparietal junctions within the radiation field (arrows).

shielding, remains unknown. Improvements in identification of the target volume and the use of three-dimensional treatment planning, as well as improvements in treatment delivery, make it possible to reduce the dose of radiation to uninvolved normal tissues to a greater extent than hitherto possible. However, whether this will result in a reduction of morbidity and permit the use of higher doses of radiotherapy, as with HRT, even if shown to be efficacious in terms of tumor control, remains to be demonstrated.

CONCLUSION

Hyperfractionated radiotherapy remains investigational in poor prognosis patients with brain stem tumors. Given the findings seen on follow-up of our long term survivors, it is important that patients with more favorable disease not be included in such studies.

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