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The role of early post radiation MRI scans in children with diffuse intrinsic pontine glioma (DIPG)

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Abstract

Purpose: To determine optimal timing of assessing post-radiation radiographic response on MRI scans in pediatric patients with diffuse intrinsic pontine glioma (DIPG).

Methods and Materials: Patients were treated on a prospective study at the National Cancer Institute (Protocol #06-C-0219) evaluating the effects of radiation therapy. Standard RT was administered in standard fractionation over six weeks. Post-radiation MRI scans were performed at 2 and 6–8 weeks.

Results: 11 patients with DIPG were evaluated. Median age was 6 yrs (range: 4–13 years). Patients were treated with EBRT to 55.8 Gy (n=10) or 54 Gy (n=1) with a GTV to PTV expansion of 1.8–2.0 cm. All patients received prescribed dose and underwent post-treatment MRIs at 2 and 6–8 weeks. Pretreatment imaging revealed compression of fourth ventricle (n=11); basilar artery encasement (n=9); tumor extension outside the pons (n=11); tumor hemorrhage (n=2). At the 2 week scan, basilar artery encasement improved in 7/9 patients, extent of tumor was reduced in 5/11 patients. Fourth ventricle compression improved in 6/11 patients but worsened in 3/11 patients. Presumed necrosis was observed in 5/11 patients at 2 weeks; 1 additional patient at 6–8 weeks. There was no significant difference in mean AP and transverse diameters of tumor between the 2 and 6–8 week time points. 6/11 patients had increasing ventricular size with no evidence of obstruction.

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Conflicts of Interest Notification:
None.

Conclusions: There is no significant difference in tumor size of DIPG patients who have received standard RT when measured at 2 weeks versus 6–8 weeks post RT. The majority of patients had the largest change in tumor size at the 2 week scan post-RT with evolving changes documented on the 6–8 week scan. 6/11 patients had progressive ventriculomegaly without obstruction, suggestive of communicating hydrocephalus. To the best of our knowledge, this is the first documentation of this phenomenon in this cohort of patients.

Keywords

pontine glioma; radiation therapy; MRI; optimal timing

Introduction

Diffuse intrinsic pontine glioma (DIPG) is a central nervous system tumor that accounts for the vast majority of pediatric brain stem gliomas. Unfortunately, DIPG has a poor prognosis with a median survival of 9–12 months even with the use of multi-modality treatment including radiation therapy and adjuvant chemotherapy (1–8). This group of patients is challenging to treat given the potential symptoms and the limited temporary improvement seen with standard treatment protocols. A small subset of patients with DIPG achieve long term survival but predicting which patients are in this group is currently impossible and the biological basis for these differences are unknown.

Children with DIPG are currently treated with radiation therapy. There has been investigation into the role of imaging characteristics both at presentation and after radiation treatment in an attempt to correlate certain findings with overall outcome, but no standard MR imaging characteristic has correlated with outcome (9–11). Liu and colleagues recently published a study comparing MRI findings at presentation with the patient's clinical response to radiotherapy but were unable to show a significant relationship (12).

All patients who receive radiation treatment are usually closely followed with conventional MRIs to evaluate treatment response or tumor re-growth. There appears to be no specific analysis of the timing of post RT imaging and as such, in our study we aimed to find the optimal timing of assessing early post-radiation radiographic response on MRI scans in pediatric patients with DIPG. Diffuse intrinsic gliomas are not typically biopsied and therapeutic decisions depend heavily on imaging to assess response to therapy. The optimal timing and specific MR sequences to best assess disease response to radiation therapy are unknown. We sought to evaluate what imaging time point was best able to assess response.

Material/Methods

Patient characteristics

Between February 2007 and March 2009, patients were prospectively enrolled on an institutional review board (IRB) approved study “An Exploratory Study of Biologic and Pathophysiologic Effects of Radiation Therapy in Pediatric Patients with Central Nervous System Tumors” at the National Cancer Institute (Protocol #06-C-0219). Eligible patients were $\geq$ 21 years of age, had a diagnosis of a CNS tumor, and no previous radiation

treatment. Patient who had previous surgery or received chemotherapeutic regimens were eligible. Among these patients, 11 newly diagnosed patients with DIPG were evaluated and treated with external beam radiation therapy (EBRT).

Treatment specifics

Prior to the first fraction of radiation therapy, all patients had imaging scans including a brain MRI. Each patient had a CT simulation for which they were placed in the supine position, an aquaplast mask was made and a planning CT scan was performed with 0.3 cm spacing between slices. The CT scans extended from the vertex to about C7 vertebrae. Using the Eclipse treatment planning system (Varian Oncology Systems, Palo Alto, CA), the treating radiation oncologist contoured the gross tumor volume with the aid of the pre-treatment MRI. The clinical target volume and the planning target volume were then created, a total of about 1.8–2.0 cm expansion from the GTV to the PTV.

The relevant organs at risk (OARs), including the brainstem, optic nerves, optic chiasm, and spinal cord were outlined by the treating radiation oncologist. Ten patients were treated to 55.8 Gy/1.8 Gy and one patient received 54 Gy/1.8 Gy. All treatment planning and optimization was performed using Eclipse (Varian Oncology Systems, Palo Alto, CA). Patients were treated on one of two Varian Clinacs (2100EX2999); both are equipped with MLC-120 multi-leaf collimators.

Three of the eleven patients were treated concurrently with capecitabine and radiation treatment, three patients were treated with the farnesyltransferase (FTase) inhibitor, tipifarnib, and three additional patients were enrolled on a phase II trial studying the use of interferon alpha in the post radiation treatment setting.

MRI Imaging

All patients had baseline imaging brain MRI performed within two weeks prior to beginning radiation therapy. MRI was performed on a 1.5 T scanner with a standard quadrature head coil. Prior to contrast administration, axial FLAIR, axial T2-weighted, and axial T1-weighted sequences were obtained. Additional sequences, including investigational sequences (dynamic susceptibility contrast-enhanced perfusion (DSC), 3D T1 fast spoiled gradient, diffusion tensor imaging, and ^1H -NMRS), were performed as time permitted.

Follow-up

Follow-up brain MRI scans were performed after the completion of radiation treatment per protocol at 2 weeks and again 6–8 weeks post treatment.

For this study, the images were read by one neuroradiologist and the measurements were performed in one sitting using side by side images.

Median follow-up was defined as the time from date of registration to last follow-up visit. Overall survival was defined as the time from the date of registration to the date of death.

Results

At diagnosis, median age was 6 yrs (range: 4–13 years). Six of the patients were female. All patients successfully completed treatment (received the prescribed dose of radiation) and underwent post treatment MRIs at 2 weeks and 6–8 weeks.

At a median follow-up of 7.7 months, the median survival was 11.2 months. Baseline MR imaging characteristics are displayed in Table 1.

Clinical findings

Presenting symptoms varied but, most commonly, patients presented with gait instability, headaches and cranial nerve (CN) abnormalities. Clinical symptomatic improvement was seen in all 7 patients who had a decrease in tumor size at the 2 week scan. Of those patients, one had an increase in tumor size at the 6–8 week scan and had correlating symptoms of unsteady gait and worsening CN abnormalities at that time period. Three patients had slightly increased tumor size at the 2 week scan and two of those three patients had worsening neurologic symptoms. One patient had stable tumor size with overall stable symptoms. We found that in our group of patients there was correlation between MRI findings and symptoms post treatment at 2 weeks.

Imaging findings at initial presentation

At baseline, all patients showed infiltrative masses involving the pons, with extrapontine extension noted in all cases. The extrapontine extension was most commonly seen in the midbrain followed by the medulla and upper cervical spine. The infiltrative tumors showed increased signal on T2 and FLAIR images with decreased signal on T1 weighted images, as expected. Initial enhancement was noted in all but two patients; in three patients the enhancement was very subtle. Mild necrotic changes were noted in at least five patients on presentation and no necrosis was noted at initial presentation or any time point in three patients. Basilar artery encasement was seen at presentation in all but two cases. Hemorrhage was noted initially in two patients. The fourth ventricle was compressed or impinged upon to different extents in all patients on presentation. Finally, initial enhancement was noted in all but one patient.

Comparison of early (2 week) and late (6–8 week) MRI scans

At the 2 week scan time point, the extent of tumor was improved in 7/11 patients and these changes were not significantly different in 6/7 patients at the 6–8 week scan. Changes in tumor size are described in detail in Table 2. In addition to the tumor size, we noted other imaging characteristics that had changed from presentation. Basilar artery encasement was improved in 7/9 patients. Two patients did not show any initial encasement but one showed significant encasement at 6–8 weeks. Fourth ventricle compression was improved in 6/11 patients but worsened in 3/11 patients. Three patients who had necrotic changes noted on initial presentation, exhibited slight worsening at two weeks; one patient had further worsening seen at the 6–8 week scan. No worsening of original necrotic changes was noted in two patients on follow-up scans. Of note, six of the eleven patients had progressively increasing ventricular size and no other evidence of obstruction.

Discussion

Diffuse intrinsic pontine glioma is an aggressive disease with an unfortunate outcome. Patients are traditionally diagnosed and followed using conventional brain MRIs. MRIs afford us excellent anatomical detail and provide us with a non-invasive method of evaluating changes from treatment or tumor. While there have been attempts to correlate certain MRI changes prior to treatment with outcome, an association has not been appreciated. Patients continue to receive MRIs after treatment as a way of monitoring their response but currently there is no guidance in the timing of these scans.

In our protocol, we had the unique opportunity to evaluate pediatric patients with DIPG at two time points within 8 weeks after radiation treatment with the objective of assessing post-treatment changes in tumor size. We found that the majority of patients had the greatest change in size evident at the two week scan post-radiation treatment with evolving changes continuing through the 6–8 week scan. In our limited study we find that a conventional MRI at an earlier time shows changes evident at two weeks after completing the treatment regimen may be indicative of the longer term changes that progress at the six to eight week scan. We also noticed that six of our eleven patients had progressive ventriculomegaly without evidence of distal obstruction, which could be due to communicating hydrocephalus.

Previous studies have shown variability in tumor measurements among experienced readers (13) and in an attempt to minimize this potential confounding factor, we had a single reader perform all the measurements with all three time points side by side.

Conclusion

In this group of patients with an unfortunate prognosis, limiting post treatment scans would be ideal. In our study we discovered that changes in tumor size seen at the 2 week scan did not change significantly at the 6–8 week scan demonstrating that a post treatment scan can be performed anytime within those weeks and that no one time point during this window is most optimal. The note of progressive ventriculomegaly in these patients is, to the best of our knowledge, first documentation of this phenomenon in the medical literature for this cohort of patients. Gaining some additional insight into these findings and how tumors behave in various imaging techniques is just one of the many the steps to understanding pediatric CNS tumors better. It is our hope that this knowledge will eventually assist in designing patient specific treatments, assessing therapy response and characterizing histopathologic characteristics of these tumors. Further study will be necessary to further investigate and understand this change.

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Highlights

We evaluated a subset of patients with diffuse intrinsic pontine glioma (DIPG) who were treated on a prospective study evaluating the effects of radiation therapy. We had the unique opportunity to image patients with diffuse intrinsic pontine glioma (DIPG) at baseline and then again at 2 weeks and 6–8 weeks post radiation treatment. The majority of patients had the largest change in tumor size at the 2 week scan post-RT with evolving changes documented on the 6–8 week scan. We found that in our group of patients there was correlation between MRI findings and symptoms post treatment at 2 weeks. There was note of progressive ventriculomegaly in these patients, which is to the best of our knowledge, first documentation of this phenomenon in the medical literature for this cohort of patients

(From Left to Right) Axial FLAIR, axial T1 and enhanced-axial T1 weighted images at baseline (A), two weeks after radiotherapy (B) and six weeks after radiotherapy (C). Decreased size of the pontine infiltrative mass on FLAIR images is noted between A and B with slight further changes seen on C (White arrows). Note the appearance of hemorrhagic changes within the mass on the second examination with some worsening on the third examinations (white block arrows).

Table 1.

Baseline MRI tumor characteristics

Tumor Characteristics	Patients (n=11)
Fourth ventricle compression	11
Basilar artery encasement	9
Tumor extension beyond pons	11
Tumor hemorrhage	2

Table 2.

Changes in tumor size

		Pre-treatment MRI	2 week post RT MRI	6–8 week post RT MRI
Patient 1	AP diameter	38 mm	33 mm	33 mm
	transverse diameter	54 mm	53 mm	45 mm
Patient 2	AP diameter	45 mm	54 mm	55 mm
	transverse diameter	56 mm	59 mm	57 mm
Patient 3	AP diameter	30 mm	35 mm	35 mm
	transverse diameter	43 mm	49 mm	46 mm
Patient 4	AP diameter	33 mm	33 mm	34 mm
	transverse diameter	43 mm	43 mm	45 mm
Patient 5	AP diameter	38 mm	28 mm	39 mm
	transverse diameter	48 mm	24 mm	41 mm
Patient 6	AP diameter	41 mm	34 mm	30 mm
	transverse diameter	54 mm	44 mm	41 mm
Patient 7	AP diameter	33 mm	29 mm	30 mm
	transverse diameter	43 mm	37 mm	39 mm
Patient 8	AP diameter	39 mm	24 mm	20 mm
	transverse diameter	54 mm	30 mm	30 mm
Patient 9	AP diameter	32 mm	20 mm	21 mm
	transverse diameter	50 mm	30 mm	30 mm
Patient 10	AP diameter	54 mm	39 mm	28 mm
	transverse diameter	48 mm	42 mm	32 mm
Patient 11	AP diameter	37 mm	41 mm	38 mm
	transverse diameter	33 mm	44 mm	34 mm