Predicting outcome of children with diffuse intrinsic pontine gliomas using multiparametric imaging

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Noninvasive evaluation using MRI is the primary means to routinely assess children with diffuse intrinsic pontine gliomas (DIPGs). However, no standard MR sequence has correlated with outcome in these patients. In this study, patients with DIPGs were assessed to determine the combined prognostic value via dynamic susceptibility contrast (DSC) MRI, single-voxel spectroscopy (SVS), multivoxel MR spectroscopy (MRS), and T1-weighted post-gadolinium imaging. Eligible patients had clinical and radiographic findings consistent with a DIPG. Imaging studies were acquired on a 1.5T MRI at various time points during each patient’s course. Data were evaluated using a Cox proportional hazard model, a time-dependent covariant Cox model, a Wald test, and a Kaplan–Meier analysis. Ninety-eight studies were performed on 34 patients of median age 5.5 years. Median survival from diagnosis was 468 days. At baseline imaging only, increased ratio of choline to N-acetylaspartate (Cho:NAA) on SVS and increased perfusion on DSC-MRI each predicted shorter survival (relative risk [RR] = 1.48, \( P = .015 \) and RR = 4.91, \( P = .0012 \), respectively). When analyzing all subsequent time points, increased maximum Cho:NAA on MRS (RR = 1.45, \( P = .042 \)), increased Cho:NAA on SVS (RR = 1.69, \( P = .003 \)), increased perfusion (RR = 4.68, \( P = .0016 \)), and the presence of enhancement (RR = 5.69, \( P = .022 \)) each predicted shorter survival. Kaplan–Meier analysis showed shorter survival associated with increased perfusion at baseline (\( P = .0004 \)). Increased perfusion at any time point predicts a significantly shorter survival in children with DIPG. In addition, enhancement, increased Cho:NAA on SVS, and increased maximum Cho:NAA on chemical shift imaging are predictive of shorter survival over time. Routine baseline and subsequent imaging for children with DIPG should, at minimum, incorporate DSC-MRI and SVS.

Keywords: diffuse intrinsic pontine glioma, MR spectroscopy, pediatric, prognosis, susceptibility perfusion.

Brain tumors are the most common solid neoplasm in childhood and the second most common group of pediatric cancers. Brainstem gliomas are 10%–20% of all CNS tumors in the pediatric population, with 80% being diffuse intrinsic pontine gliomas (DIPGs). Median survival from diagnosis for children with a DIPG is approximately 9–12 months, and no significant increase in survival has been demonstrated with chemotherapy.

It is standard of care to diagnose DIPGs based on MRI findings in the context of a typical clinical presentation. Tissue biopsy is not routinely performed due to the critical location of these tumors. The most common clinical presentation includes the triad of cranial neuropathies, ataxia, and long tract signs. MRI findings include a large expansive pontine lesion that is hypointense or isointense on T1-weighted imaging, hyperintense on T2-weighted and fluid-attenuated...
Inversion recovery (FLAIR) imaging, and of variable enhancement with gadolinium-based contrast agents. Management of patients with DIPGs, therefore, relies on noninvasive evaluation methods, primarily imaging. MRI is the standard imaging modality due to its superior resolution and lack of radiation exposure. However, routinely evaluated imaging characteristics, such as tumor size, edema, enhancement, and presence of hydrocephalus have not been prognostic in these patients. In addition, standard MRI sequences cannot always distinguish treatment effects from disease progression and give no information regarding tissue metabolism.

Newer MR sequences have been developed and are being incorporated into the evaluation of patients with brain tumors. MR spectroscopy (MRS) is a method to noninvasively evaluate specific metabolites in tissue. Choline (Cho), N-acetylaspartate (NAA), lactate, lipids, and creatine are the most common metabolites identified at long echo times. Different patterns of metabolite concentrations are associated with increased cellular growth, necrosis, and normal tissue. Studies have shown that increased ratio of Cho to NAA (Cho:NAA) is associated with malignancy. In a study evaluating multivoxel MRS in children with recurrent, progressive CNS tumors, maximum Cho:NAA (i.e., worst voxel) >4.5 was associated with shorter survival compared with lower ratios. Several spectroscopy techniques, including single-voxel and multivoxel, are available, and each has advantages and disadvantages.

Dynamic susceptibility contrast (DSC) MRI is a noninvasive sequence to evaluate the blood volume in a region of interest (ROI). Increased blood volume in a tumor may be indicative of increased vascular growth and has been associated with higher grade in CNS tumors. Studies have indicated that lower-grade gliomas have decreased blood volume in comparison with higher-grade gliomas.

This study was performed to determine whether combining results from multiple MR sequences would better predict the outcome of patients with DIPG and whether such sequences could potentially serve as surrogate markers of response or disease progression.

**Methods**

**Patients**

Patients in this study were evaluated by a protocol approved by the National Cancer Institute (NCI) Institutional Review Board. All patients had a brainstem mass consistent with a DIPG (i.e., a mass involving >50% of the pons, being hypo or isointense on T1-weighted imaging or hyperintense on T2-weighted imaging, having an epicenter in the pons, involving the ventral pons, and having no primary exophytic component). Clinical findings included, but were not limited to, cranial nerve deficits, ataxia, weakness, headaches, and long tract signs. Patients were <19 years of age at the time of their initial evaluation.

Data were acquired prospectively and longitudinally at different points and time intervals in the disease course. Imaging intervals were determined by the patient’s clinical status, treatment protocol, and MRI scanner availability. Each imaging session included standard MR sequences, single-voxel spectroscopy (SVS), MRS, and DSC-MRI. No acquisition time exceeded 120 min per imaging session. Clinical data were documented and retrieved from the NCI electronic medical record.

The patient’s first MRI session that acquired all imaging sequences was considered the baseline for the purposes of this study.

**MRI, Spectroscopy, and Susceptibility Perfusion Acquisition**

All imaging was performed on a Signa HDx 1.5T scanner (GE Medical Systems). MRI and MRS sequences were acquired using a standard quadrature head coil. We performed the following imaging: pre- and postcontrast T1-weighted spin echo (repetition time [TR]/echo time [TE] = 450/13 ms, 50 slices, slice thickness = 3 mm), T2-weighted fast spin echo (TR/TE = 3400/95 ms, 53 slices, slice thickness = 3 mm), and FLAIR (TR/TE/inversion time = 10 000/140/2200 ms, 53 slices, slice thickness = 3 mm).

SVS was obtained using a point-resolved spectroscopic sequence (PROBE-P, GE Medical Systems) with automated shimming and water suppression (TR/TE = 1500/144 or 270 ms, field of view [FOV] = 22 × 22 cm, slice thickness = 15 or 20 mm). Acquisition time was 3.5 min. Voxels were prescribed graphically from a T2-weighted image and placed for maximum coverage of the tumor within the pons, posterior to the basilar artery. Areas of CSF, bone, and subcutaneous fat were not included.

Multislice MRS imaging was acquired using a slice-selective spin echo sequence (TR/TE = 2300/280 ms, FOV = 24 × 24 cm, matrix = 32 × 32, 4 slices, slice thickness = 15 mm, slice spacing = 3 mm) with 8 outer volume suppression pulses to suppress lipid signals from the scalp and skull, and a chemical shift-selective water suppression pulse. Acquisition time was 20 min. Minimal voxel size was 7.5 mm × 7.5 mm × 15 mm (0.84 cm³). MRS slices were acquired using the same locations as a T1-weighted axial oblique spoiled gradient echo localizer sequence (TR/TE = 50/3.5 ms, slice thickness = 15 mm, slice space = 3.5 mm). The MRS slices were aligned so that the center of one slice included the maximum tumor diameter within the pons.

DSC-MR images were acquired after the MRS sequences were performed. The contrast agent gadopentetate dimeglumine (Gd-DTPA) was used at a dose of 0.1 mmol/kg after normal renal function was confirmed by age-appropriate creatinine values. DSC-MRI sequence was acquired using a gradient echo sequence (TR/TE = 1500/90 ms, 51 slices, slice thickness = 5 mm, slice space = 0 mm, fractional anisotropy = 90°, FOV = 22 cm, matrix = 128 × 128). Auto shimming with phase correction was performed.
**Data Processing**

All standard imaging was reviewed with a neuroradiologist on a picture archiving and communication system (PACS) workstation. Presence or absence of enhancement was determined qualitatively by the changes between the T1-weighted pre- and postcontrast images and documented as a binary value.

Single-voxel spectral data were reconstructed using GE scanner software, and images were transferred to our institution’s PACS database. Metabolite information was recorded and used to calculate Cho:NAA ratios. The presence of lactate and lipids was defined as peaks located at 1.33 parts per million with amplitudes greater than 3 times baseline noise amplitude. Raw MRS data were processed on a Linux workstation using a customized software package developed in Interactive Data Language (ITT Visual Information Solutions). The software provided automated selection of metabolite peaks and generated metabolite signal intensity maps for NAA, Cho, and creatinine. Pre-contrast FLAIR images were imported and registered to multivoxel slice locations. ROIs were selected manually on FLAIR images and metabolite signal intensity maps. Analysis software automatically evaluated the quality of ROI spectra using previously described criteria. Voxel with insufficient lipid or water suppression were excluded from further analysis. Quality control was reviewed by a spectroscopist. Using the area under the signal intensity peak, relative metabolite concentrations for Cho and NAA were calculated and recorded as Cho:NAA ratios. Maximum Cho:NAA for each ROI was identified using a “worst voxel” analysis, as described by Warren et al. (2000).

DSC-MRI analysis was performed on the GE Advantage Workstation (version AW4.1.06) using the Functool 2 application (version Functool 2.6.0). DSC-MR images were coregistered with the standard MR images and qualitatively assessed by a neuroradiologist. Perfusion imaging was determined to be successful if there was an adequate integral curve through the ROI that was located in the pons. The neuroradiologist used the cerebral blood volume map fused and linked to both the nonenhanced and enhanced T1-weighted images obtained at the same level on a PACS workstation. The choroid plexus and the basilar artery were localized on the enhanced images and care was taken not to interpret increased perfusion corresponding to these structures as abnormal. The 3 sequences (DSC-MRI, T1, and enhanced T1-weighted) were evaluated concurrently along with the FLAIR images. The result was a binary value of presence or absence of increased perfusion. Normal tissue within the brain was used as an internal control, as is standard at the NCI.

**Statistics**

Analysis of the associations among perfusion, metabolites as determined by SVS and MRS, presence of enhancement, and overall patient survival were performed. Kaplan–Meier estimates were performed on the baseline perfusion data in a standard fashion using the log-rank test to determine P-values. P < .05 was considered statistically significant.

Univariate and multivariate analyses were done for baseline results using the Cox proportional hazards model for relative risk (RR) values. Only the covariates that were significant at the P < .05 level in the univariate analysis were entered into the multivariate analysis.

Baseline data were compared between patients to determine the RR of survival. Longitudinal measurements of Cho:NAA were related to survival by a Cox proportional hazards model with time-dependent covariates. As such, Cho:NAA at the first scan was treated as the baseline measurement, and the RR referred to the risk at a given time relative to baseline Cho:NAA between different patients.

The P-values were determined using the Wald test for both the univariate and multivariate analyses. P < 0.05 was considered significant. Data were analyzed using the statistical computing package R (http://www.r-project.org/).

**Results**

Ninety-eight studies were performed on a total of 34 patients: 12 male and 22 female. Two patients had not received radiation therapy prior to the acquisition of images. Parents of both families deferred radiation in favor of alternative therapies. One patient was a long-term survivor (122+ months), and the other patient survived for 13.6 months from diagnosis. Two additional patients had biopsies performed at outside institutions; both were grade II astrocytomas. At the time of the analysis, 1 patient had died at 13.7 months, and the other patient was still alive. The surviving patient died at 15.2 months, outside the time of study analysis. Time intervals between studies ranged from 28 to 784 days. Patients were followed for a median of 108 days, with a range of <30 days to 1,260 days. Median overall survival from diagnosis was 468 days (95% confidence interval: 434–775) (Table 1).

**Baseline (Single Time Point) Analysis**

Univariate analysis of baseline imaging demonstrated that both increased SVS Cho:NAA ratios and increased perfusion had statistically significant RR of shorter survival (RR = 1.48 and P = .015, and RR = 4.91 and P = .0012, respectively). Maximum MRS Cho:NAA, presence of lipid-lactate peaks, and presence of enhancement at baseline were not predictive of shorter survival (Table 2).

Only the covariates that were significant at the P < .05 level in the univariate analysis were entered into the multivariate analysis. Therefore, multivariate analysis was performed using only the SVS Cho:NAA and perfusion results obtained at baseline. Increased perfusion on DSC-MRI was statistically significant when combined (RR = 3.04, P = .04), but increased SVS Cho:NAA was not significant (RR = 1.41, P = .21) (Table 2).

Perfusion at baseline imaging was evaluated as a potential prognostic factor for shorter survival using
Kaplan–Meier survival curve estimates (Fig. 1). Patients with increased perfusion at baseline as determined by DSC-MRI had shorter survival compared with patients with normal or decreased pontine perfusion (P = .0004).

Longitudinal Analysis

Increasing Cho:NAA (for SVS and MRS) meant that an individual patient had a higher Cho:NAA value during the course of follow-up. The statistical interpretation was based on an individual's increases in Cho:NAA and RR for shorter survival. Univariate analysis of changes in imaging parameters over time showed that increasing maximum Cho:NAA determined by MRS (RR = 1.45, P = .042), increasing Cho:NAA on SVS (RR = 1.69, P = .003), increased perfusion (RR = 4.68, P = .0016), and presence of enhancement (RR = 5.69, P = .022) significantly predicted shorter survival (Table 2). The presence of lipid-lactate on SVS was not predictive of shorter survival by univariate analysis.

For longitudinal imaging parameters, 4 covariates from the univariate analysis—namely, MRS maximum Cho:NAA, SVS Cho:NAA, increased perfusion on DSC-MRI, and enhancement—were significant (P < .05) and were entered into the multivariate analysis. The multivariate analysis did not demonstrate statistical significance to combined MR parameters (Table 2).

Table 1. Clinical and imaging data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, n (%)</th>
<th>Median (range)</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (35%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22 (65%)</td>
<td></td>
</tr>
<tr>
<td>Age at dx (y)</td>
<td></td>
<td>5.5 (1.6–14.6)</td>
</tr>
<tr>
<td>&lt;3</td>
<td>4 (12%)</td>
<td></td>
</tr>
<tr>
<td>3–10</td>
<td>23 (68%)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>7 (20%)</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dx to RT</td>
<td>32 (94%)</td>
<td>14 (6–1559)</td>
</tr>
<tr>
<td>RT dose</td>
<td>32 (94%)</td>
<td>54 (50.4–61.2)</td>
</tr>
<tr>
<td>MRI studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies per patient</td>
<td>34 (100%)</td>
<td>2 (1–18)</td>
</tr>
<tr>
<td>Dx to first scan*</td>
<td>34 (100%)</td>
<td>18 (9–410)</td>
</tr>
<tr>
<td>RT to first scan*</td>
<td>32 (94%)</td>
<td>8 (1–87)</td>
</tr>
<tr>
<td>Baseline spectroscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVS Cho:NAA</td>
<td>34 (100%)</td>
<td>2.11 (0.68–5.92)</td>
</tr>
<tr>
<td>MRS Cho:NAA</td>
<td>34 (100%)</td>
<td>2.16 (0.66–6.31)</td>
</tr>
</tbody>
</table>

Abbreviations: dx, diagnosis; RT, radiation therapy; SVS, single-voxel spectroscopy; Cho:NAA, ratio of choline to N-acetylaspartate; MRS, multivoxel MR spectroscopy.

*First scan represents the first scan in which all advanced imaging sequences (DSC perfusion, SVS, and MRS) were performed with interpretable results used in this analysis and may not represent the first MRI performed on study.

Table 2. Imaging analysis

<table>
<thead>
<tr>
<th></th>
<th>Baseline imaging</th>
<th>Longitudinal imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UA</td>
<td>MA</td>
</tr>
<tr>
<td>Maximum MRS Cho:NAA</td>
<td>1.09</td>
<td>–</td>
</tr>
<tr>
<td>Increased SVS Cho:NAA</td>
<td>1.48*</td>
<td>1.41</td>
</tr>
<tr>
<td>Presence of lipid-lactate</td>
<td>2.32</td>
<td>–</td>
</tr>
<tr>
<td>Increased DSC-MRI</td>
<td>4.91**</td>
<td>3.04*</td>
</tr>
<tr>
<td>Presence of enhancement</td>
<td>2.14</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: UA, univariate analysis; MA, multivariate analysis; MRS, multivoxel MR spectroscopy; Cho:NAA, ratio of choline to N-acetylaspartate; SVS, single-voxel spectroscopy; DSC, dynamic susceptibility contrast.

*P < .05.

Kaplan–Meier survival curve estimates (Fig. 1). Patients with increased perfusion at baseline as determined by DSC-MRI had shorter survival compared with patients with normal or decreased pontine perfusion (P = .0004).

Discussion

Children with DIPGs are notoriously difficult to treat, and survival rates are poor. Treatments for this type of tumor are constantly under investigation, but none have demonstrated a significant impact on overall survival of a study cohort. However, several studies have reported sporadic cases of patients who do have prolonged survival. Identification of those patients with better or worse prognosis may aid in treatment decisions.

In lieu of biopsy, MRI techniques are used in order to characterize the tumor and determine treatment decisions, despite any prior correlation with prognosis. As more advanced MR sequences become available, their role in the management of patients with a DIPG needs to be better defined. This study demonstrates the importance of obtaining 3 sequences at baseline and longitudinally, namely post-contrast T1-weighted imaging, DSC-MRI, and SVS.

While combining results from different MR sequences in a multivariate fashion is difficult and statistically does not add information, analysis of individual sequence results may assist in treatment decision
making. Baseline DSC-MRI and SVS studies demonstrating increased perfusion and Cho:NAA, respectively, are associated with shorter survival. Increased perfusion at any time point was the most prognostic indicator. However, evaluating changes in perfusion over time is difficult, as results are generally qualitative rather than quantitative. In contrast, changes in Cho:NAA over time, as determined by either SVS or MRS, were prognostic and can therefore potentially be used as indicators of response or lack of response to treatment.

Although this study demonstrates a significant prognostic value of certain MR sequences, there are potential limitations. Voxel placement for SVS at different time points was operator dependent and varied with the changes in tumor over time. DSC-MRI and MRS acquisition and analysis are not standardized. Because of the absence of tissue acquisition, it was not possible to validate whether enhancement was due to necrosis or tumor growth. Additionally, the absence of pathology in most of the patients in this study may confound the data by including patients with lower-grade histology, like a pilocytic astrocytoma. Clinical and imaging criteria are the standard for DIPG diagnosis, but the lack of pathologic correlation increases the possibility that a lower-grade lesion may be entered into a clinical protocol geared to evaluate higher-grade tumors. Although radiographically homogeneous, the patient population was heterogeneous in regard to treatment and time points of evaluation. This is a bias that occurs with large referral centers similar to the NCI. Studies evaluating newly diagnosed patients treated on the same regimens throughout their disease course are under way at our institution to address this issue.

This study is the first to demonstrate the prognostic value of specific MR sequences for patients with DIPG. Perfusion as determined by DCS-MRI appears to be a robust independent prognostic indicator, and efforts to standardize the acquisition and analysis of these data would be worthwhile to validate this in a large group setting. Although Cho:NAA as determined by SVS was somewhat prognostic, the value of Cho:NAA is in the determination of changes over time and potential associations with response or progression. Based on our results, baseline SVS (PROBE-P sequence or similar sequence) and DSC-MRI should be incorporated into standard MR imaging of this patient population.

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**References**


