Metastatic Low-Grade Gliomas in Children: 20 Years’ Experience at St. Jude Children’s Research Hospital

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Background. Patients with low-grade gliomas (LGG), which are the most common childhood brain tumors, have excellent long-term survival. Dissemination of LGG is rare. Robust data on the incidence, presentation, patterns of dissemination, disease behavior, outcome, and best-management approaches do not exist. We describe 20 years of follow-up of children with metastatic LGG.

Procedure. Data collected during the period 1990–2010 were retrospectively reviewed for the following inclusion criteria: diagnosis of metastatic LGG, age younger than 21 years at initial diagnosis, and magnetic resonance imaging of the brain and/or spine at diagnosis and/or follow-up. Patient demographics, pathology, treatment modalities, and outcome were reviewed.

Results. Of 599 patients with LGG, 38 (6%) had metastatic disease at either diagnosis or follow-up. Most tumors (87%) were located in the brain, and half of the patients had metastatic disease at presentation. The most common diagnosis was pilocytic astrocytoma (55%). Chemotherapy was the most common initial treatment modality. Median survival of the group was 6.2 years (range, 0.1–16.9 years). Fifteen (40%) patients died at a median of 6 years from diagnosis (range, 0.8–15 years). Overall survival at 5, 10, and 15 years was 80.7 ± 6.6%, 63.0 ± 10.2%, and 50.9 ± 16.0%, respectively.

Conclusion. This study describes the longest follow-up of children with metastatic LGG. LGG is underestimated and entails major morbidity and mortality. Prospective studies are needed to learn the true incidence, study the biology, and determine the best approaches to diagnosis, treatment, and follow-up.

INTRODUCTION

In children, low-grade gliomas (LGG) are the predominant central nervous system (CNS) tumor; they constitute 35–55.5% of childhood CNS tumors.[1–5] According to the World Health Organization (WHO), LGG are classified based on the cell of origin and tumor grade.[6] They are characterized by indolent progression, and patients usually have an excellent probability of long-term survival with the current treatment approaches.[4,7,8]

LGG can disseminate along the neuraxis, either at diagnosis (2–5%) or at the time of disease progression (5–12%).[9–55] This phenomenon was described in the literature long before the magnetic resonance imaging (MRI) era.[9,10,12] However, limited data are available on the true incidence, presentation, patterns of dissemination, disease behavior, outcome, and best-management approaches to treating metastatic LGG. These gaps in knowledge led to inconsistent conclusions about the outcome of patients with metastatic LGG. Most reports suggest favorable outcome, although not as good as LGG without metastatic spread.[33,37,53,56] This is in large part due to the fact that most of the information has been derived from small series (fewer than 10 cases in most series),[9,10,12,15,19,20,23,24,27,30,33–37,43,45,50,52,55] and case reports.[11,14,16,18,21,22,25,26,28,29,31,32,38–41,44,46–48,51,54]

In addition, the largest series to date (two series included 13 patients each and one included 61 patients) reported a relatively short-term follow-up (i.e., 5 or 10 years),[33,37,53] which could have biased the results, given the slow progression of the disease. Finally, the current standard of care for patients with LGG does not systematically include a complete MRI workup at diagnosis (as was done in our study); thus, we cannot exclude the possibility that some patients with LGG have silent metastases.

In this study, we describe 38 patients with metastatic LGG at diagnosis or at a later time point during follow-up that were treated at our institution during a 20-year period. Our study demonstrates that long-term follow-up of patients with LGG reveals worse prognosis than previously believed and warrants more indepth analysis of this understudied disease.

METHODS

Retrospective Review

The study was reviewed and approved by the Institutional Review Board at St. Jude Children’s Research Hospital. We reviewed the database of all patients treated by the Division of Neuro-Oncology at our institution between January 1990 and December 2010. The date of diagnosis was selected as the date of the first surgery that obtained tissue for diagnosis or the date of the first MRI examination in cases where biopsy was not performed. All patients with the following criteria were included in the study: diagnosis of LGG according to the WHO classification, age younger than 21 years at diagnosis, and the presence of metastatic disease.

Key words: long-term follow-up; low-grade glioma; metastatic; overall survival

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; CSI, craniospinal irradiation; GG, gangliogioma; GTR, gross-total resection; HC, hypothalamic/chiasmatic; JPA, juvenile pilocytic astrocytoma; LGG, low-grade glioma; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; NOS, not otherwise specified; NTR, near-total resection; ODG, oligodendroglioma; OS, overall survival; PA, pilocytic astrocytoma; PFS, progression-free survival; PMA, pilomyxoid astrocytoma; PXA, pleomorphic xanthoastrocytoma; RFNGT, rosette-forming glioneuronal tumor; STR, subtotal resection; WHO, World Health Organization

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disease either at diagnosis or at a later time point during follow-up (based on MRI findings). Diagnosis of LGG without tissue confirmation was accepted in cases in which the primary tumor site was the optic nerve, hypothalamus/optic chiasm (HC), or tectum. Primary tumor location (brain versus spine) was determined based on the location of the main tumor mass. Demographic, clinical, laboratory (cerebrospinal fluid [CSF] analysis), surgical, radiologic, pathologic, and outcome data were collected. Tumors were categorized based on their locations: supratentorial, infratentorial, or spinal.

The extent of surgical resection was assigned to one of the four categories based on the surgeon’s report and postoperative images: (1) gross-total resection (GTR), no visible tumor remaining in the surgical field; (2) near-total resection (NTR), removal of more than 90% but less than 100% of tumor; (3) subtotal resection (STR), removal of 50–89% of the tumor; or (4) biopsy, removal of less than 50% of the tumor.

Initial treatment (chemotherapy, observation, surgery, radiation therapy) was defined as the primary modality of therapy that was administered after diagnosis and prior to disease progression. Surgery was considered the primary treatment modality when it was not followed by other treatment modalities (i.e., chemotherapy or radiation therapy) until disease progression.

Statistical Analyses

The overall survival (OS) was calculated as the time from the date of initial diagnosis to the date of death or the last follow-up. Progression-free survival (PFS) was calculated as the time from the date of initial diagnosis to the date disease progression was detected or the date of last follow-up. Kaplan–Meier method was used to estimate the OS and PFS. The Cox proportional hazard model was used to explore the associations of covariates with OS and PFS.

RESULTS

Patient Demographics

A total of 599 patients with the diagnosis of LGG were identified. Among those patients, 38 (6.3%) had metastatic disease (Table I). Median age at diagnosis was 4.9 years (range 1.5 months–20.6 years). We had a slight male predominance in our study (21 male patients and 17 female patients). Most were of the white race (n = 50). Only one patient had a diagnosis of neurofibromatosis type 1 (NF1), based on the NIH criteria. This patient had a midline pilocytic astrocytoma (PA) with secondary dissemination to the brain. The study cohort is summarized in a flow chart (Fig. 1).

Primary Disease Location and Dissemination

At diagnosis, 16 (42%) patients had a complete neuraxis evaluation (i.e., MRI of brain and spine); 20 (52.6%) had an MRI evaluation of the brain only; two (5.2%) had an MRI of the spine only, and both of those patients had metastatic disease. Of the two patients who had only spinal MRI examinations at diagnosis, one had a brain MRI within 2 months after diagnosis that demonstrated cranial metastatic disease. All but one patient had an MRI examination of the spine at later follow-up. Only one patient did not have a full neuraxis evaluation during the study period. This patient experienced metastatic disease in the brain at 41 months from diagnosis. All other patients had a full neuraxis evaluation either for metastatic workup (MRI spine [n = 17], MRI brain [n = 1]) after the discovery of new metastatic lesions (n = 8), routine metastatic workup at the physician’s discretion (n = 5), primary tumor progression (n = 4), or new clinical symptom (n = 1, abnormal gait) (Table II).

The primary tumor was located in the brain in 32 (52.6%) cases. Tumors were most commonly located supratentorially (n = 20, 52.6%), followed by the posterior fossa (n = 12, 31.6%), and spine (n = 6, 15.8%). In the supratentorial region, tumors were most frequently located in the midline HC region (n = 12, 60%).

Nineteen (50%) patients had disseminated disease at presentation (five cranial, six spinal, and eight craniospinal), and 19 (50%) experienced dissemination later during follow-up (12 cranial, three spinal, and four craniospinal) (Table III). All patients whose primary LGG was a spinal tumor also had metastatic disease at diagnosis. Five of the 19 patients with metastatic disease at diagnosis experienced secondary metastases to the spine (n = 4) or brain (n = 1). Metastatic disease was located in the brain in 15 (39.4%) patients, in the spine in eight (21.2%) patients, and in the brain and spine in 15 (39.4%) patients (Table II). Twenty-nine (76.3%) patients had leptomeningeal dissemination. Seven (18.4%) had intraparenchymal metastatic lesions, and only two (5.3%) had leptomeningeal and intraparenchymal metastatic lesions.

Surgery and Histology

At diagnosis, 17 (44.7%) patients underwent surgical resection of the primary tumor (two GTR, four NTR, and 11 STR) (Table I). Seven (41.2%) of those patients had metastatic disease at diagnosis. Eighteen (47.3%) patients had a biopsy, and three (8%) did not have tissue confirmation at diagnosis due to location of the tumor (two HC and one tectum). All three patients had a biopsy later at progression, and pathologic findings were consistent with LGG. Twelve (31.6%) patients had two surgical interventions, and one patient had three surgical interventions. For four patients, the purpose of the second procedure was to biopsy a metastatic lesion for tissue confirmation.

All tissue samples were reviewed at our institution prior to the start of therapy. Results from initial diagnostic samples, primary lesions sampled at disease progression, or metastatic lesions were confirmed. The most common diagnosis was PA (n = 23, 60.5%), followed by LGG-not otherwise specified (NOS) (n = 7, 18.4%) (Table I). None of the patients was reported to have anaplastic features. Ki67 proliferation index was reported in 14 patients (36.8%) (28 not analyzed). The majority (71.4%) had low labeling index (<3%). Two patients had minimally elevated index (3–5%), one with oligodendroglioma (ODG) experienced secondary dissemination in the spine 7 months from diagnosis, and one with juvenile pilocytic astrocytoma (JPA) had primary dissemination to the brain and spine. Ki67 varied from low to moderately elevated in different tumor sites in two patients. Both had PA with secondary dissemination to the brain or spine at 7 and 2 months from diagnosis, respectively.

Cerebrospinal Fluid Analysis

CSF analysis was performed in 16 (42%) patients: eight were done at diagnosis and eight were done at a later time point during follow-up. Eleven CSF samples were obtained via lumbar puncture (four at diagnosis and seven at follow-up); three were obtained during surgery; and two were obtained from a shunt. Only one

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## TABLE I. Patient Demographics

<table>
<thead>
<tr>
<th>LGG category</th>
<th>Pt. no.</th>
<th>Sex</th>
<th>Year of Dx</th>
<th>Age at Dx (years)</th>
<th>Pathology</th>
<th>Primary tumor location</th>
<th>PD/SD location</th>
<th>First-line treatment</th>
<th>Time to MET (months)</th>
<th>OS (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td>1 F</td>
<td>1991</td>
<td>14 PA</td>
<td>HT</td>
<td>SD&lt;sup&gt;a&lt;/sup&gt;, brain</td>
<td>RT (focal)</td>
<td>22</td>
<td>13.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 F</td>
<td>1991</td>
<td>0.3 PA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Chiasm/HT</td>
<td>SD&lt;sup&gt;b&lt;/sup&gt;, brain</td>
<td>Observation</td>
<td>41</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 M</td>
<td>1992</td>
<td>0.4 PA</td>
<td>Chiasm/Left ON</td>
<td>PD, spine</td>
<td>Observation</td>
<td>8</td>
<td>22&lt;sup&gt;+&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 M</td>
<td>1993</td>
<td>16 PA</td>
<td>HT</td>
<td>SD&lt;sup&gt;b&lt;/sup&gt;, B/S</td>
<td>Observation</td>
<td>26</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 M</td>
<td>1993</td>
<td>5.7 LGG-NOS</td>
<td>HT</td>
<td>PD, B/S</td>
<td>Chemo (carbo/vcr)</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 M</td>
<td>1993</td>
<td>3.4 PA</td>
<td>HT</td>
<td>SD, spine (2 m)</td>
<td>Observation</td>
<td>2</td>
<td>8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 F</td>
<td>1994</td>
<td>13.3 PA</td>
<td>Right thalamus</td>
<td>SD&lt;sup&gt;b&lt;/sup&gt;, brain</td>
<td>Surgery (STR)</td>
<td>9</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 M</td>
<td>1995</td>
<td>9.9 ODG</td>
<td>Right temp lobe</td>
<td>SD&lt;sup&gt;b&lt;/sup&gt;, brain</td>
<td>Chemo (carbo/tamoxifen)</td>
<td>8</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 M</td>
<td>1996</td>
<td>0.9 PA</td>
<td>Chiasm/HT</td>
<td>PD&lt;sup&gt;d&lt;/sup&gt;, brain</td>
<td>Chemo (carbo/VCVR)</td>
<td>0</td>
<td>15.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 M</td>
<td>1999</td>
<td>3.3 PA</td>
<td>HT, thalamus, Optic pathway</td>
<td>SD&lt;sup&gt;d&lt;/sup&gt;, brain</td>
<td>Chemo (carbo/VCVR)</td>
<td>0</td>
<td>6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 M</td>
<td>2001</td>
<td>5.4 GG</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; and left lateral ventricles</td>
<td>SD&lt;sup&gt;d&lt;/sup&gt;, brain</td>
<td>Chemo (carbo/vp16/cyclo)</td>
<td>11</td>
<td>6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 M</td>
<td>2001</td>
<td>8.5 PXA</td>
<td>Left temp lobe</td>
<td>SD&lt;sup&gt;d&lt;/sup&gt;, brain</td>
<td>Surgery (GTR)</td>
<td>70 (brain)</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 M</td>
<td>1996</td>
<td>1.7 PA</td>
<td>Bilateral ONs, Chiasm/HT</td>
<td>SD&lt;sup&gt;d&lt;/sup&gt;, brain</td>
<td>Chemo (carbo/vcr)</td>
<td>57</td>
<td>16.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 M</td>
<td>2001</td>
<td>1.7 PA</td>
<td>Right thalamus, Right insula</td>
<td>SD&lt;sup&gt;d&lt;/sup&gt;, brain</td>
<td>Surgery (NTR)</td>
<td>8</td>
<td>1.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 F</td>
<td>1999</td>
<td>0.7 PA</td>
<td>Chiasm/HT</td>
<td>SD&lt;sup&gt;d&lt;/sup&gt;, B/S</td>
<td>Chemo (carbo/vcr)</td>
<td>36</td>
<td>5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 F</td>
<td>2005</td>
<td>0.5 PA</td>
<td>Bilateral ONs, optic chiasm, optic radiations</td>
<td>SD&lt;sup&gt;d&lt;/sup&gt;, brain</td>
<td>Observation</td>
<td>23</td>
<td>8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 M</td>
<td>2008</td>
<td>11 PA</td>
<td>Foramen of Luschka</td>
<td>PD, B/S</td>
<td>RT (CSI)</td>
<td>0</td>
<td>6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 M</td>
<td>2008</td>
<td>2.8 DA</td>
<td>Right temp lobe</td>
<td>PD&lt;sup&gt;d&lt;/sup&gt;, brain, SD, spine (3 m)</td>
<td>Chemo (carbo/vcr)</td>
<td>0 (brain)</td>
<td>6.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 M</td>
<td>2008</td>
<td>10.8 DA</td>
<td>Right temp lobe</td>
<td>PD&lt;sup&gt;d&lt;/sup&gt;, brain, SD, spine (3 m)</td>
<td>Chemo (carbo/vcr)</td>
<td>0 (brain)</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 M</td>
<td>2010</td>
<td>5.5 PA</td>
<td>Chiasm/HT</td>
<td>PD&lt;sup&gt;d&lt;/sup&gt;, brain, SD, spine (1 m)</td>
<td>Chemo (TPCV)</td>
<td>0 (brain)</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Infratentorial | 21 F | 1990 | 20.6 PA | BS | PD, spine | RT (CSI) | 0 | 0.9 |
| | 22 M | 1993 | 0.1 ODG | BS | SD<sup>d</sup>, brain | Surgery (NTR) | 7 | 21.2 |
| | 23 F | 1998 | 12.3 PA | 4<sup>th</sup> ventricle | SD<sup>d</sup>, brain | Surgery (NTR) | 120 | 20.7<sup>+</sup> |
| | 24 F | 2000 | 6.7 PA | 4<sup>th</sup> ventricle | SD<sup>d</sup>, B/S | Surgery (STR) | 96 | 14.5<sup>+</sup> |
| | 25 F | 2002 | 2.3 PA | BS | SD, brain | RT (focal) | 33 | 3.7 |
| | 26 F | 2003 | 11.7 PA | BS | SD<sup>d</sup>, brain | Surgery (STR) | 10 | 10.4<sup>+</sup> |
| | 27 F | 2005 | 2.9 LGG-NOS | 4<sup>th</sup> ventricle | PD, spine | n.a. (treatment at another facility) | 0 | 0.1<sup>b</sup> |
| | 28 F | 2006 | 2.1 PA | 4<sup>th</sup> ventricle | PD, B/S | Chemo (vcr/carbo/tmx) | 0 | 8.6 |
| | 29 M | 2005 | 2.8 LGG-NOS | Tectum/segmentum | PD<sup>d</sup>, brain, SD spine (15 m) | Observation | 0 (brain) | 8.6 |
| | 30 F | 2006 | 1.1 PA | BS | SD, spine | Surgery (STR) | 2 | 7.7 |
| | 31 M | 2008 | 6.1 LGG-NOS<sup>c</sup> | Tectum | SD, brain | Observation | 9 | 6.4 |
| | 32 F | 2008 | 13.3 GG | 4<sup>th</sup> ventricle | PD, B/S | RT (CSI) | 0 | 5.7 |
| | 33 F | 1993 | 5.1 PA | Spine | PD, B/S | RT (CSI) | 0 | 10.5 |
| | 34 M | 2000 | 7.1 PA | Spine | PD, B/S | Chemo (carbo/vcr) | 0 | 13.4 |
| | 35 M | 2004 | 3.2 LGG-NOS | Spine | PD, B/S | RT (CSI) | 0 | 7 |
| | 36 M | 2004 | 8.9 LGG-NOS | Spine | PD, B/S | Surgery (NTR) | 0 | 10.4 |
| | 37 F | 2004 | 4.9 RFGN | Spine | PD<sup>d</sup>, B/S | Chemo (carbo/vcr) | 0 (brain) | 6 |
| | 38 M | 2003 | 2.3 LGG-NOS | Spine | PD<sup>d</sup>, spine | Chemo (carbo/vcr/tmx) | 0 | 10.9 |

B/S, brain and spine; carbo, carboplatin; CSI, craniospinal irradiation; cyclo, cyclophosphamide; DA, diffuse astrocytoma; Dx, diagnosis; GG, ganglioglioma; GTR, gross-total resection; HT, hypothalamus; LGG-NOS, low-grade glioma not otherwise specified; MET, metastasis; n.a., not applicable; NTR, near-total resection; ODG, oligodendroglioma; ON, optic nerve; PA, pilocytic astrocytoma; PD, progressive disease; PXA, pleomorphic xanthoastrocytoma; RFGN, rosette-forming glioneuronal tumor; RT, radiation therapy; SD, stable disease; STR, subtotal resection; temp, temporal; tmz, temozolomide; TPCV, thioguanine/procarbazine/CCNU/vincristine; ver, vincristine; vp16, etoposide.

<sup>a</sup>MRI of the spine not done at diagnosis. <sup>+</sup>Lost to follow-up. <sup>b</sup>Pathology not done at diagnosis. <sup>c</sup>MRI of the spine not done at any time point.
patient had tumor cells in the CSF collected by lumbar puncture. Another patient who had undergone lumbar puncture at diagnosis had suspicious cells but was later deemed negative after treatment. The level of CFS proteins was elevated in nine of 16 (56.2%) patients, including the patient with tumor cells in the CSF. Spinal MRIs indicated disease in seven of the nine patients. In most of the patients with elevated CSF proteins, the values trended down with treatment response and up with disease progression.

**Treatment Outcome**

Chemotherapy was the initial treatment modality in 14 (36.8%) patients. Most of the regimens were carboplatin based. Surgery was the initial treatment in nine (23.7%) patients (one GTR, four STR, and four NTR). Eight of the nine patients treated with surgery had primary nonmetastatic brain tumors. One patient had primary spinal disease with leptomeningeal spread to the brain. Radiation therapy was used upfront in seven (18.4%) patients. Five patients with metastatic disease at diagnosis received craniospinal irradiation (CSI) at doses ranging from 36 to 48.4 Gy. Median age at the time of CSI was 11 years (range, 3.2–20 years). Two patients received focal radiation therapy, and both had nonmetastatic disease at diagnosis. Seven (18.5%) patients were observed as their initial therapeutic approach, and three had metastatic disease at diagnosis (two brain and one spine). All patients who were initially observed required further therapy. Treatment information was not available for one patient who was treated at another institution. All patients received at least one form of treatment, including surgery. Six patients received five forms of treatment; 16 received at least four forms; 24 received at least three forms; and 32 received at least two forms. Table I includes details about first-line treatment for all patients.

Our patients were followed for a median of 80 months (range, 1.1 month–22 years). Thirteen (34.2%) patients were followed more than 10 years. Among our study population, 20 (52.6%) patients are still alive. Three patients were lost to follow-up after 0.1, 1.4, and 13.8 years, respectively. Fifteen (39.5%) patients died at a median of 6 years from diagnosis (range, 0.8–15 years). Seven (46.7%) of those patients had metastatic disease at diagnosis, and six (40%) had midline tumors. Death occurred due to disease progression in all but one case; that patient died of infectious complications. PA was the most common diagnosis among the deceased patients; 10 patients had PA, and one patient each had the following diagnoses: pleomorphic xanthoastrocytoma (PXA), ganglioglioma (GG), ODG, rosette-forming glioneuronal tumor (RFGNT), and LGG-NOS. Primary disease was located in the brain in 12 patients and in the spine in three patients. Twelve (80%) of the deceased patients had metastatic disease at diagnosis, and eight (53%) had initial symptoms within 3 months of diagnosis. Median survival for the whole group was 6.2 years (range, 0.1–16.9 years).

![Study group flow chart](image-url)
Overall Survival and Progression-Free Survival

The OS at 5, 10, and 15 years was 80.7 ± 6.6%, 63.0 ± 10.2%, and 50.9 ± 16%, respectively (Fig. 2). The PFS at 1, 2, and 5 years was 45.9 ± 8.0%, 27.0 ± 7.0%, and 8.1 ± 3.9%, respectively (Fig. 3). No significant associations were detected between age, sex, pathology, primary tumor location, or time to metastases and OS, or PFS in the univariate Cox proportional hazard models (data not shown).

DISCUSSION

Children with LGG generally have an excellent outcome and are usually long-term survivors.[1,7,57–59] However, this does not apply to those with metastatic LGG for whom the prognosis is worse, though different studies have reported inconsistent outcomes.[33,37,53] Although metastatic LGG is a rare entity, it has been reported with increased frequency due to increased index of suspicion and the use of advanced imaging technique.[33,35,37,60] Our study is the second largest study to date, after the German HIT-LGG-1996 study,[53] which included 61 patients. Importantly, our study provides the longest follow-up of metastatic LGG in children to date and documents a high mortality rate. In the HIT-LGG-1996 study,[53] the median follow-up was 68.9 months (range, 2.8 months–14.9 years), and the 5-year OS was 73%.[53] Hukin et al. reported a total of 26 patients in two separate studies.[33,37] The median follow-up of 74 months (range, 29 months–12 years) in their study of metastatic LGG at diagnosis and 60 months (range, 5 months–14.6 years) in their study describing metastatic LGG at progression. The 5- and 10-year OS were both 68% in patients with metastatic disease at progression. They reported one death in a patient with metastatic disease at diagnosis. The OS in our study was favorable at 5 years (80.7±6.6%); however, it dropped remarkably to 63.0±10.2% and 50.9±16% at 10 and 15 years,
respectively. This is the worst outcome for metastatic LGG to be reported.

We believe the main reason for the high mortality rate in our study is the very long follow-up compared to that reported by others. The 5-year PFS in our study was 8.1% ± 3.9%. In line with our results, Von Hornstein et al. reported 5-year PFS of 6% in a subgroup of patients who received chemotherapy.[53] Hukin et al. reported 5-year PFS rates of 17% and 15% in children with primary or secondary metastatic LGG treated with different chemotherapies alone or in combination with radiotherapy.[33,37,53]

It is unclear at this point how and why dissemination of LGG occurs. Some pathology (e.g., pilomyxoid astrocytoma) may be more prone to dissemination than other LGG subtypes,[53] but malignant transformation,[26] tumor location,[23,35,43,53] type of surgical procedures,[35,43] age younger than 1 year at diagnosis,[53] and shunt placement[28] may also play a role. However, evidence is not sufficient to prove these theories.[13,20,23,28,35,43] Tumor biology may be a key factor in dissemination.

Unfortunately, data about the molecular biology of metastatic LGG are almost nonexistent. Tabori et al. investigated six cases of metastatic LGG; they found a high rate of epidermal growth factor receptor gene amplification and protein expression compared to those measures in nonmetastatic control group samples.[45]

Metastatic disease was present in nearly half of our patients at either diagnosis or a later time point during follow-up, which is similar to the published data (Supplementary Table I). [9–16,18–41,43–48,50–55] The median time to dissemination was 11 months, which is also comparable to data in the literature. [9–55] We did not detect differences in OS due to age at diagnosis, primary versus secondary dissemination, histologic subtypes, or male versus female sex, which is similar to the findings in Von Hornstein’s study.[53] This might be due to the relatively small sample size of our study population.

As for primary tumor location, previous reports suggest that patients with involvement of the HC region are at higher risk of disease dissemination and death.[16,20,23,53] Mamelak et al. showed that metastatic disease is 23 times more likely to develop in children with PA in the HC region than it is in patients whose primary tumors are in other locations.[19] This might be explained by the proximity of the tumor to the subarachnoid space and the third ventricle and the difficulty of performing GTR in that region.[16,20,23] Dissemination of hemispheric LGG is rare and usually occurs in children aged 8 years or older.[19,23,33,37,53] HC locations were the most common in our series (n = 13, 40.6%). Almost half of our patients with primary midline disease succumbed to their disease. Although statistically insignificant, which was probably because of the small number of patients, this finding supports the reported increased risk of dissemination and worse prognosis in patients with tumors in the midline locations.[16,20,23,35,53]

Age younger than 1 year at diagnosis is an important factor related to dissemination of LGG.[20,23,27,33,35,37,53,56] The German study demonstrated a 16% incidence of dissemination.
among infants with remarkable male preponderance.[53] This could be related to the frequent association of HC location and young age. In addition, these patients usually do not receive radiation as part of their initial therapy.[35] Almost 40% of our patients with primary tumors in the HC region were infants at diagnosis. Thus, our numbers were not large enough to draw conclusions about any relation between age and prognosis.

In our series, the most common histologic diagnoses were PA and LGG-NOS. Similarly, most reports in the literature describe uses of PA. [9–11,13–16,19–21,24,26,28,30,31,35,36,38–41,43,46,47,52,55, 56] This reflects the natural incidence of these tumors in children; PAs account for a quarter of all pediatric brain tumors, and LGG-NOS represents nearly one-third of all pediatric LGG.[1,2] Ki67 is an antigen that reflects the proliferative activity of the tumor. Higher values are usually associated with more aggressive tumors. No data on the correlation of Ki67 with LGG dissemination are available, and correlations with OS and PFS are controversial.[61,62] Ki67 proliferation analysis was performed in about one-third of our cases; thus, we were not able to draw any conclusions due to the small number. In their study, Hornstein et al. analyzed the Ki67 proliferation index in 39 patients but were not able to detect any association with OS or event-free survival.[53] Although reports of other LGG subtypes are substantially less frequent, they suggest that certain subtypes are more aggressive and more prone to dissemination than PA, mostly PA with myxoid features or pilomyxoid astrocytoma (PMA). [3,35,53,63] PMA is a relatively new histopathologic entity that is seen in children younger than 3 years and usually involves the HC region.[35] It was first described in 1999 and was not included in the WHO classification until 2007.[6,53,63] This is probably the cause of our underestimation of this LGG subtype in the previous reports, as well as in the current study. One patient in our series experienced malignant transformation at 1.7 years from diagnosis and died almost 3 years from diagnosis. In the literature, two patients were reported to experience malignant transformation at 7 and 35 years from diagnosis.[14,39] It is hypothesized that malignant transformation contributes to dissemination of LGG; however, this theory has not been proven due to the rarity of cases.[26]

One patient in our study had NF1. This is not surprising, as LGG dissemination is not known to occur in patients with NF1. None of the 109 patients with NF1 from the HIT-LGG-1996 study had disseminated disease.[64]

CSF analysis for malignant cells and protein is not routinely performed in patients with LGG because positive results are so infrequent, even in cases of spinal dissemination.[20] In our series, only one patient who had spinal dissemination at diagnosis also had malignant cells in the CSF. Another patient with nonmetastatic disease at diagnosis had suspicious cells. Intracranial metastatic lesions developed in that patient 8 months after diagnosis, but spinal metastasis never occurred. Both patients had negative CSF at follow-up after treatment was initiated. Our literature review identified 16 CSF samples that were positive for malignant cells among 46 evaluated samples.[9,11,12,15,17,20,22–24,26,28,34–37,46,50,51,53,55]

Protein in the CSF was elevated in 10 (62.5%) of the 16 evaluated cases, including the case with positive CSF. Three samples were obtained at diagnosis; the rest were obtained at later time points during follow-up. The median protein level was 147.5 mg/dl (range, 81–2005 mg/dl; normal value in our laboratory, 12–0 mg/dl). Our literature review revealed four reported cases with elevated protein in the CSF; none of them had neoplastic cells.[22,34,51,55] Although the number of samples was not sufficient for analysis, we observed a trend of decreased protein level with response to treatment and increased protein level during recurrences. This has not been discussed in literature, but we believe this is an important point to pursue in the future, as this can be a good surrogate marker for early detection of metastatic disease and monitoring of treatment response. Confounding factors that might give false-positive results (e.g., traumatic tap, infection, presence of a shunt) must be taken into consideration when interpreting CSF protein results, as they may affect the analysis.

The goal of treating patients who have metastatic LGG must be to control the disease with minimal toxicity. Deferral of radiation therapy, especially CSI, is also very important especially in younger patients.[53] Currently, there is no consensus on first or subsequent types of treatment that should be administered to patients with metastatic LGG.[53,56] Platinum-based regimens, especially in combination with vincristine, are most commonly used in LGG and may lead to long-term survival, delay of radiation therapy, and prolonged PFS.[8,65] The same regimens are generally used to treat patients with metastatic disease.[12,20,33,35,37,53,56] Analysis of treatment efficacy in metastatic LGG has not given robust conclusions, as it is mostly based on small retrospective series.[53] In the study by Von Hornstein et al., most of the patients received the same therapy with carboplatin and vincristine. Only a small proportion received focal radiation therapy and was not sufficient for analysis. The overall response rate (including stable disease) was 76%, and the median time to progression from start of chemotherapy was 16.9 months.[53] Response to therapy was comparable between primary and metastatic sites.[53,66] Similarly, in our study, the median time to disease progression from initial treatment with chemotherapy was 16 months, as opposed to 8, 7, and 6.5 months for those whose initial treatments were observation, surgery, and radiation therapy, respectively. The differences between these values were not statistically significant, which may be related to the small number of patients and the nonuniform treatment regimens used. Chemotherapy is the preferred first-line treatment modality in metastatic LGG; this approach helps avoid or at least delay CSI, given that many of these patients are very young and would suffer from devastating long-term side effects of that treatment.[19,30,35,56]
Study Limitations

Our study was limited by several factors, including its retrospective nature, relatively small number of patients, the lack of molecular biology analysis, and a nonuniform treatment approach.

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REFERENCES


