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Overview

Benefits of radiosurgery for patients include the ease of a one day outpatient treatment with focused high dose radiation, which can be used for unresectable disease at initial presentation, localized recurrent disease, and metastatic disease with excellent normal tissue sparing. The role of radiosurgery for pediatric tumors is not well established. The available retrospective evidence demonstrates utility for some children with primary brain tumors resulting in good local control and imaging response. However, the potential toxicities are unique and not insignificant. Small recurrent or residual pilocytic astrocytomas may make ideal targets for radiosurgery. The available series of radiosurgery for pediatric low-grade gliomas comprise both grade I and grade II tumors, utilize a range of radiosurgery doses, and demonstrate local control in the range of 70.8 to 100%, with follow-up ranging from 19 to 144 months. I propose this multicenter project to the IGKRF to more clearly define the outcomes and associated toxicities of radiosurgery for pilocytic astrocytoma and develop a thoughtful treatment paradigm for utilizing radiosurgery for these tumors.

Background

Radiosurgery utilizes precise immobilization, high definition imaging, multiple intersecting beams to create an extremely conformal radiotherapy plan consisting of 1-5 high-dose treatments with rapid dose fall off and sparing of adjacent normal tissues. It is a standard treatment approach for adults with brain
metastases and intracranial benign brain lesions.\textsuperscript{8-10} The utility of radiosurgery is not as well documented for predominantly pediatric brain tumors. For pilocytic astrocytoma, radiosurgery may have an important role for treating unresectable tumors, residual disease, or tumors in the recurrent setting that have received prior radiotherapy.

Maximal safe resection is the initial treatment of choice for most brain tumors. The extent of resection is known to be prognostic for low-grade glioma.\textsuperscript{11} However, location of tumors in eloquent areas can make tumors unsafe to resect and negatively impact progression free survival.\textsuperscript{11}

Adjuvant conventional fractionated radiotherapy improves local control for most pediatric brain tumors however this may come at the cost of long-term side effects which include neurocognitive deficits\textsuperscript{12,13}, endocrine deficiencies\textsuperscript{14}, growth deficits\textsuperscript{14}, reduced hearing\textsuperscript{15}, risk for secondary malignancy\textsuperscript{16,17}, and radiation necrosis.\textsuperscript{18,19}

Pediatric low-grade gliomas are a heterogeneous group of tumors located most commonly in the cerebellum followed by the cerebral hemispheres as well as deep midline structures such as the hypothalamus, thalamus, lateral and 3rd ventricles, corpus callosum, and the visual pathway. Collectively, they comprise approximately 26\% of childhood CNS malignancies in the US.\textsuperscript{20} Observation after gross total resection is standard of care and results in progression-free survival from 80\% for Grade II tumors to more than 90\% for Grade I tumors.\textsuperscript{21} Adult pilocytic astrocytoma are rare, but prospective data suggests equally good outcomes.\textsuperscript{22} Tumors may demonstrate an indolent natural history after incomplete resection, but progression-free survival at 5 years is only 55\% as reported from the Children’s Cancer Group/Pediatric Oncology Group low grade glioma trial.\textsuperscript{23}

Indications for radiosurgery for pediatric low-grade glioma have included surgically inaccessible tumors and as adjuvant treatment for incompletely excised or recurrent tumors. The available series of radiosurgery for pediatric low-grade gliomas comprise both grade I and grade II tumors and
demonstrate local control in the range of 70.8 to 100%, with follow-up ranging from 19 to 144 months\(^1\). Many of these patients also had prior radiotherapy. Radiosurgery was found to be safe and well tolerated with smaller tumors having improved local control.\(^4\),\(^7\)

One series of 24 patients with 12 years follow-up demonstrated that the median time to documented decrease in tumor size was 12.5 months; however some patients did not respond until more than 40 months after treatment and yet they still achieved a complete response.\(^7\) Of note, this series included WHO grade I, II and III patient with both upfront residual disease and recurrent disease. At last follow up, a decrease in tumor size of at least 50% was demonstrated in 18 patients (75%) and complete tumor resolution was achieved in 5 (21%).

The main treatment related complication was transient symptomatic tumor edema which was reported in several series of radiosurgery for pediatric low-grade glioma,\(^2\),\(^3\),\(^5\),\(^7\) otherwise no additional toxicity was reported, including radiation necrosis. Kida et al., \(^5\) reported an increase risk of transient tumor edema for grade II compared to grade I gliomas. In a series with the highest reported incidence of temporary tumor edema or cyst growth, 44% (7 out of 16 patients), only 19% (3 out of the 16) were symptomatic.\(^2\) These imaging changes were seen up to 28 months after the radiosurgery procedure.\(^3\)

It is not possible to directly compare the outcomes of these retrospective series, which include a heterogenous group of patients with prospective series utilizing fractionated radiotherapy. However, radiosurgery for treatment of pediatric low-grade gliomas with a range of indications appears to be relatively safe with good local control and imaging response. Transient symptomatic treatment related edema was the main toxicity observed.

**Purpose**

The purpose of this study is to define the outcomes, related toxicity, and ideal patient population for radiosurgery for pilocytic astrocytoma.
Specific Aims

1. Define the long term efficacy of Gamma Knife radiosurgery for pilocytic astrocytoma.
2. Define the toxicity of Gamma Knife radiosurgery for pilocytic astrocytoma.
3. Analyze the impact of pretreatment factors on the efficacy and toxicity of Gamma Knife radiosurgery for pilocytic astrocytoma.
4. Define the role of Gamma Knife radiosurgery for pilocytic astrocytoma.

Eligibility

1. Patients with a histologically proven diagnosis of pilocytic astrocytoma.
2. Patients must have received Gamma Knife radiosurgery as a component of their treatment.

Data Collection

Data will be collected using a standardized spreadsheet. Clinical factors will include date of diagnosis, patient age at diagnosis, patient date of birth, gender, KPS, tumor location. Pretreatment factors will include date and extent of surgical excision, adjuvant therapies including chemotherapy dates and types, any fractionated radiotherapy including dates, total dose, and dose fractionation. Radiosurgery information will include indication, treatment date, tumor location, tumor size (volume and max diameter), prescription dose, prescription isodose line, dose conformity, dose heterogeneity, number of shots, and maximum dose. Clinical outcome will include date of last clinical follow up, date of last imaging follow up, date of progression, location of progression (local versus distant), date of death. Toxicity data will be collected including date, time from GKRS, and CTCAE grade.

Statistical Analysis

Efficacy data will be evaluated using the Kaplan-Meier analysis to determine local control and event free survival from the time of Gamma Knife radiosurgery. The effect of pretreatment factors and treatment variables on treatment outcome and toxicity will be analyzed using univariate and multivariate analyses. Analyses will be conducted using the R statistical software package (R Core Team 2015. R Foundation for Statistical Computing, Vienna Austria). Statistical significance will be determined using a two-sided P-value of less than 0.05.

Table I. Radiosurgery for Pediatric Low-Grade Glioma

<table>
<thead>
<tr>
<th></th>
<th>No pts</th>
<th>Prior RT</th>
<th>Tumor Size*</th>
<th>Marginal dose (Gy)</th>
<th>Follow up (mo)</th>
<th>Control</th>
<th>Toxicity (No. of pts with symptomatic edema)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barcia 1994</td>
<td>16</td>
<td>12</td>
<td>NA</td>
<td>21.7</td>
<td>NA</td>
<td>81%</td>
<td>NA</td>
</tr>
<tr>
<td>Boëthius 2002</td>
<td>16</td>
<td>2</td>
<td>3.3 cm³</td>
<td>11.3</td>
<td>102</td>
<td>100%</td>
<td>7</td>
</tr>
<tr>
<td>Hadjipanayis 2002</td>
<td>37</td>
<td>10</td>
<td>3 cm³</td>
<td>15</td>
<td>28</td>
<td>92%</td>
<td>2</td>
</tr>
</tbody>
</table>
Kano 2009  & 50 & 5 & 2.1 cm³ & 14.5 & 55.5 & 70.8% & NA \\
Kida 2000  & 12 & 25.4 mm & 12.5 & 27.6 & 91.7% & 1 \\
Somaza 1996  & 9 & 2 & 16 mm & 15 & 19 & 100% & 0 \\
Weintraub 2012  & 24 & NA & 2.4 cm³ & 15 & 144 & 96% & 3

Abbreviations: No = number, pts = patients, RT = radiotherapy, NA = not available.

*Tumor size is given as median volume or maximal dimension

References


