Revisiting the Role of Radiation Therapy for Pediatric Low-Grade Glioma

Danielle S. Bitterman, MD[1,2,3]; Shannon M. MacDonald, MD[2]; Torunn I. Yock, MD[2]; Nancy J. Tarbell, MD[2]; Karen D. Wright, MD, MS[4]; Susan N. Chi, MD[4]; Karen J. Marcus, MD[3]; and Daphne A. Haas-Kogan, MD[3]

Case

An 11-year-old boy presented with right eye vision loss. Imaging showed an optic pathway tumor. Over 7 years, he was treated with multiple courses of systemic agents, including vincristine and carboplatin; actinomycin-D and vincristine; bevacizumab; thioguanine, procarbazine, lomustine, and vincristine plus bevacizumab; everolimus; and trametinib. Over the years, he developed progressive right eye vision loss and left temporal visual field cut, cerebrovascular accident due to the tumor, and hemorrhagic hydrocephalus requiring multiple shunt revisions. Intraventricular biopsy after an episode of hemorrhagic hydrocephalus confirmed low-grade glioma (LGG). He was referred to radiation oncology in hopes that radiation therapy (RT) would quell ongoing neurologic decline, but he herniated before starting treatment because of disease progression. Surgical decompression was deemed unsafe. In keeping with the family and patient's goals of care, active interventions were discontinued, and the patient died comfortably at home shortly thereafter.

Background

We are all too familiar with such patients with pediatric LGG requiring multiple systemic agents over the course of their lifetime. We counsel families that this is a survivable disease; yet, for this patient and others, that is not always the case. Has the pendulum swung too far away from consideration of RT as a valid treatment modality for such patients? Broad avoidance of RT because of fear of toxicities puts patients at high risk for morbidity and mortality from tumor progression, even when RT may be an excellent, tolerable salvage option.

Pediatric LGGs account for approximately one third of pediatric brain tumors and should be curable cancers.[1] Historically, RT was the primary treatment of unresectable, progressive LGG, offering 10-year progression-free survival (PFS) and overall survival (OS) rates of approximately 70% and 80%, respectively.[2-5] Yet, long-term survivors suffered late RT-related consequences, particularly young patients treated to large volumes in eloquent regions of the brain. As effective chemotherapies[6-10] and targeted agents[11-13] were developed, the trend shifted toward delaying and/or avoiding RT, and its associated toxicities,[14,15] such that now its use in LGG often presents controversy.

Over the past several decades, important advances in RT planning and delivery have provided for more precise radiation delivery to the tumor, with sparing of normal structures,[16-18] translating to lower expected toxicity rates than observed historically.[19-22] We revisit RT outcomes in the modern era to update the risk-benefit analysis of its use for this curable disease.

Historical Rationale for Avoiding RT

Previously reported RT-related toxicities for pediatric LGG include cerebral vasculopathy,[23,24] second malignancy,[24,25] neurocognitive deficits,[26] and endocrine dysfunction,[27] with more devastating effects in children younger than 10 years of age.[24,26] Concerningly, upfront RT has been associated with inferior survival in administrative databases, although selection bias limits interpretation.[28,29] Yet, these toxicities should not overshadow the morbidity of tumor progression. Tsang et al[24] found pre-RT chemotherapy to be associated with worse event-free survival compared with initial RT, suggesting that the strategy of delaying RT with chemotherapy may not be entirely benign.

Advances in RT for Pediatric LGG

These concerning toxicity profiles are largely from experiences of patients treated in the era of 2-dimensional (2D) RT, which was the primary technique from the 1970s through the early 1990s. Radiation delivery has become significantly more precise since then, with smaller, conformal treatment fields and magnetic resonance imaging–based coregistration with RT planning computed tomography scans providing precise localization.[19,30] In the 1990s, 3-dimensional conformal external beam RT (3D-CRT) became standard, and in the 2000s, intensity-modulated RT (IMRT) became widely adopted. In addition, proton RT, which has minimal exit radiation dose,[16,17] is increasingly available, and its use in pediatric populations is increasing.[31-33] Studies of children with LGG treated with modern RT techniques, not those of

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patients treated in the 2D era, should inform shared decision making for patients with unresectable symptomatic and/or progressive disease.

Fractionated stereotactic RT planning that allows steep dose falloff was an early advance assessed in pediatric LGG. Marcus et al[34] performed a prospective study of stereotactic RT for pediatric brain tumors 5 cm or less, including 50 patients with LGG, ages 2 to 26 years, enrolled from 1992 to 1998. With a median follow-up of 6.9 years in the LGG cohort, 5- and 8-year PFS rates were 82.5% and 65%, respectively, and 5- and 8-year OS rates were 97.8% and 82%, respectively, indicating favorable tumor control. There were no marginal failures, which are near misses just outside the high-dose radiation field, demonstrating that this more conformal technique does not carry increased risk of local failure. Toxicities included one second malignancy and four patients with moyamoya syndrome.

Between August 1997 and August 2006, Merchant al[35,36] carried out a phase II trial of conformal fractionated RT that accrued 78 pediatric patients with LGG (ages 2.2-19.8 years) using a 10 mm clinical tumor volume (CTV) margin. In this trial, 96% of patients were treated with 3D-CRT, and 4% of patients were treated with IMRT. Invaluably, cognitive and neuroendocrine outcomes were prospectively evaluated for 5 and 10 years after RT, respectively.[36] With a median follow-up of 89 months, the 5- and 10-year event-free survival rates were 87.4% and 74.3%, respectively, and the 5- and 10-year OS rates were 98.5% and 95.9%, respectively, with only one marginal failure. The proportion of patients without symptoms increased during and after RT for all symptoms except appetite and fatigue. Improvements in vomiting, headache, and vision were most dramatic. Notably, the percent of children without visual symptoms rose from approximately 30% pre-RT to more than 90% post-RT. Five patients developed new imaging evidence of vasculopathy after RT, with children younger than 5 years old at greatest risk. One second malignancy was reported. The only significant decline in cognitive scores was in spelling. However, younger age was associated with both lower pre-RT cognitive score and greater rate of decline over time, with the most marked decline in children younger than 5 years old. The 10-year cumulative incidences of thyroid hormone and growth hormone replacement, the most common hormones affected by RT, were 64% and 48.9%, respectively. Patients with LGG treated with conformal techniques also had relatively stable emotional,[37] behavioral,[37] and adaptive[38] functioning. These results suggest that the neuropsychiatric adverse effects seen today are likely improved over those seen in the 2D era of RT, particularly in older children.

RT techniques have continued to advance, and currently, almost all patients receiving photon RT receive IMRT, not 3D-CRT. The recent Children's Oncology Group phase II study, ACNS0221 (ClinicalTrials.gov identifier: NCT00238264), evaluated conformal RT using an even smaller CTV margin of 5 mm in 85 patients with LGG, ages 3 to 21 years, from 2006 to 2010.[39] Seventy-one percent of patients received IMRT in the ACNS0221 study[39]; thus, results were more reflective of what one would expect with treatment today. At a median follow-up of 5.2 years, 5-year PFS was 71%, and 5-year OS was 93%, with no marginal failures. Reported late toxicities included tumor necrosis in one patient, causing several grade 3 neurologic adverse effects, acute visual loss that reversed with steroids in one patient, and acute diplopia that reversed with steroids in one patient. A smaller retrospective study of 39 patients, ages 1 to 17 years, treated with IMRT, also reported favorable disease control and low toxicity, with one patient receiving special education and no reported patients with blindness or second cancers at a median follow-up of 81 months.[40]

Proton RT has been shown to improve quality of life and may be more cost effective than photon RT for patients with pediatric brain tumors.[41,42] A single institutional review of patients with LGG treated with protons from 1995 to 2007, with a median follow-up of 11 years, demonstrated 8-year PFS and OS of 82.8% and 100%, respectively.[43] In a subset of patients with neurocognitive assessments, there was no decrease in neurocognitive function overall, but a decline was seen in children younger than 7 years old and those with higher volume of dose to the left temporal lobe or hippocampus. Importantly, 83.3% of patients with tumors near the optic pathways had stable or improved visual acuity after treatment. Two patients developed moyamoya syndrome. This year, Indelicato et al[44] reported results of a prospective study of 174 patients with LGG, ages 2 to 21 years, treated with proton RT with a 5-mm CTV margin, from 2007 to 2017. With a median follow-up of 4.4 years, 5-year local control, PFS, and OS were 85%, 84%, and 92%, respectively. Four percent of patients developed a serious late toxicity, including brainstem necrosis requiring steroids (n = 2), symptomatic vasculopathy (n = 2), radiation retinopathy (n = 1), epilepsy (n = 1), and a secondary high-grade glioma causing death (n = 1). A new central hormone deficiency occurred in 22% of patients. In addition, four patients developed partial sensorineural hearing loss, and six patients had asymptomatic vasculopathy in the treatment volume. Thus, proton RT seems to be effective with tolerable toxicities, although follow-up is too short to evaluate second malignancy risk. Because of their dose-sparing effects, protons, if available, should be considered when RT is recommended for pediatric LGG, given their tendency to occur near eloquent areas of the brain and the expected long survival of these children.

Systemic Agents for Pediatric LGG

Although systemic agents generally offer long-term disease control inferior to RT,[10] they have been used to replace or delay RT because of their better toxicity profile. A clear understanding of available systemic treatment options is critical, and the decision to avoid or delay RT must be weighed against the risk of worsening cancer-related

morbidity. For unresectable disease, the most well-established first-line agents are vincristine and carboplatin or single-agent vinblastine, with thioguanine, procarbazine, lomustine, and vincristine falling out of favor because of secondary malignancy risk. Over time, chemotherapy has been used in broader populations, first in patients younger than 60 months of age,[7] then in patients younger than 10 years of age,[8,9] and now routinely in patients older than 10 years of age.[10,45] Despite the shifts, there are no robust, long-term data on the comparative efficacy or neuroendocrine or cognitive adverse effects of such approaches.

The understanding of molecular drivers of oncogenesis in pediatric LGG has grown substantially, enabling development of investigational targeted agents. Most significant has been the finding of frequent alterations in the *BRAF* gene and aberrations in the MAPK signaling pathway.[46,47] Inhibitors of BRAF, such as dabrafenib and vemurafenib, and of MEK, including trametinib and selumetinib, have shown encouraging responses in case reports and early-phase trials.[13,48,49] Other targeted agents, including bevacizumab, lenalidomide, and everolimus, are often used in the second- or third-line setting. Although targeted agents are promising, their efficacy and adverse effect profiles are not well defined.[46]

Weighing Treatment Modalities in Unresectable Pediatric LGG

Balancing treatment modalities in unresectable pediatric LGG remains a significant clinical challenge. As in this patient, children are often treated with multiple lines of systemic agents, including investigational targeted agents, whereas RT is avoided because of fear of toxicity despite long-term evidence of its efficacy. Moreover, LGGs exist that are unresponsive to standard chemotherapy and for which we do not have targeted agents. The risk of RT should be weighed against the risk of tumor progression and an honest assessment of our level of understanding of the efficacy and risks of additional lines of systemic agents. Decision making should take into account the patient's baseline function, age, tumor size and location, clinical course, and presence of prognostic and/or targetable molecular aberrations. Scenarios in which RT should be considered in favor of systemic agents include older children who have failed multiple lines of systemic agents and patients with rapidly progressive tumors threatening function or life. In addition, surgical debulking or biopsy, when feasible, can be considered when it may provide a molecular diagnosis, improve symptoms, or provide a bridge to definitive treatment.

Conclusion

The rapid advances in RT and the long latency of toxicity complicate assessment of contemporary technologies.[50] Nevertheless, current RT options for pediatric LGG likely reduce toxicities compared with historic techniques, as supported by the most modern prospective studies of conformal photon[39] and proton[44] RT for pediatric LGG published this year. Although systemic agents should remain standard early treatment of most patients with unresectable or progressive pediatric LGG, this approach must be reevaluated and modern RT considered when tumor progression risks an outcome worse than any likely RT-related toxicity. Given the complex patient-specific decision making required for these patients, treatment should be discussed in a multidisciplinary setting. As we gain a better understanding of the molecular underpinnings of this disease, we will move toward a curative targeted agent with minimal acute or long-term adverse effects.

AFFILIATIONS

[1]Harvard Radiation Oncology Program, Boston, MA
[2]Massachusetts General Hospital, Boston, MA
[3]Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA
[4]Dana-Farber Cancer Institute and Boston Children's Hospital, Boston, MA

CORRESPONDING AUTHOR

Daphne A. Haas-Kogan, MD, Department of Radiation Oncology, Dana-Farber Cancer Institute, DA-16-22, 450 Brookline Ave, Boston, MA, 02115; e-mail: dhaas-kogan@bwh.harvard.edu.

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Danielle S. Bitterman
Employment: Spouse is an employee at Agios Pharmaceuticals (I)
Stock and Other Ownership Interests: Agios Pharmaceuticals (I)

Torunn I. Yock
Consulting or Advisory Role: Huron Consulting Services
Research Funding: ProTom, Elekta, MIM Software

Nancy J. Tarbell
Patents, Royalties, Other Intellectual Property: Spouse is an editor for UpToDate (I)

Karen D. Wright
Honoraria: Takeda Oncology
Consulting or Advisory Role: Infinite MD, Grand Rounds, Boehringer Ingelheim
Research Funding: Takeda Oncology (Inst)
Travel, Accommodations, Expenses: Takeda Oncology

Susan N. Chi
Consulting or Advisory Role: Epizyme
Travel, Accommodations, Expenses: Epizyme

Daphne A. Haas-Kogan
Leadership: CellWorks
Consulting or Advisory Role: Leidos Biomedical Research, Sanofi, SRA International, Gerson Lehrman Group, Guidepoint Global
Research Funding: Novartis (Inst)
Expert Testimony: Hallberg Law, Law Offices of Craig Cook

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