PEDIATRIC ONCOLOGY

Tackling Pediatric Low-Grade Gliomas: A Global Perspective

Daniel C. Moreira, MD, MEd[1,2]; Catherine G. Lam, MD, MPH[1,2]; Nickhill Bhakta, MD, MPH[1,2]; Frederick A. Boop, MD[1]; Jason Chiang, MD, PhD[3]; Thomas E. Merchant, DO, PhD[4]; Carlos Rodriguez-Galindo, MD[1,2]; Amar Gajjar, MD[2]; and Ibrahim Qaddoumi, MD, MSc[1,2]

In 2018, the WHO launched the Global Initiative for Childhood Cancer (GICC) in partnership with the global childhood cancer community. This innovative program aims to achieve at least a 60% survival for pediatric cancer patients worldwide by 2030, with the potential to save a million lives and reduce suffering for all children with cancer.[1] Low-grade glioma (LGG) is one of the six index cancers selected by the GICC to demonstrate increasing access to quality care for children with cancer, seeking to recognize and strengthen the needed multisectoral and multidisciplinary connections across health systems for children with cancer. Importantly, LGG was intentionally selected as the most common pediatric CNS tumor and because of good expected outcomes. Furthermore, the efficacy of multimodal therapy, including chemotherapy and radiation, and to promotion multidisciplinary engagement, especially with neurosurgery, was also valued.

CNS tumors represent approximately 20% of pediatric cancer cases worldwide and are the leading cause of cancer-related morbidity and mortality.[2,3] Historically, CNS tumors have received less attention and prioritization on a global scale because of the complexity of the resources required for their diagnosis and treatment, with comprehensive care requiring the integration of multidisciplinary actions that encompass accurate diagnosis and staging, access to neurosurgery, radiotherapy, and chemotherapy, and the ability to monitor for acute complications and long-term sequelae. On the basis of the existing data from population-based cancer registries, the incidence and survival of patients with pediatric CNS tumors have the widest variability of all pediatric malignancies.[2,4]

Pediatric LGGs are slow-growing tumors and, as such, can have a protracted clinical presentation. Delays in diagnosis for LGGs are frequent in all resource settings because of the vague symptoms that may occur over many months.[5] Furthermore, underdiagnosis is an important issue as it has been recently suggested that almost half of the children who develop cancer are never diagnosed.[6] Educating health care professionals about the clinical presentation of pediatric CNS tumors is essential as first-contact providers are mostly frequently presented with the initial complaints and must keep the possibility of CNS tumors in their differential diagnoses.[7] Subsequently, implementing referral networks may mitigate some of the barriers to the diagnosis of CNS tumors.[8] Nonetheless, ideal strategies to reduce delays to diagnosis without creating additional stresses on the health system, such as by increasing unneeded diagnostic tests, remain to be determined. The GICC could identify strategies, aligned with all relevant stakeholders.

LGGs frequently have good outcomes, especially when substantial surgical resection can be achieved. Children can be cured through surgery in many instances as the overall survival is >95% for children treated with gross total resection.[9] These findings underscore the critical importance of addressing neurosurgical capacity to improve outcomes for children with LGGs. A recent study to identify gaps in pediatric neurosurgical care as it relates to pediatric neuro-oncology identified disparities in the infrastructure and services needed for pediatric neurosurgeons to provide quality care for children with CNS tumors.[10] The pediatric oncology field has been inconsistent in its engagement of relevant stakeholders in neurosurgery, but this must change now across the world.

In the context of the transformation of the field of pediatric neuro-oncology, with the advent of molecular characterization to better classify CNS tumors, access to accurate and comprehensive diagnostics is essential.[11,12] The increasing gap between high- and low-resource settings in terms of the ability to offer comprehensive molecular evaluations is worth highlighting. The publication of the 5th edition of the WHO Classification of CNS Tumors in 2021 further aggravates the situation as precise classification of the many types of LGG now requires detailed molecular characterization, which is beyond reach for many low- and middle-income countries (LMICs). Although the implications of the new molecular insights on the management of pediatric CNS tumors are still being defined, strategies to increase the availability of quality neuropathologic evaluations can optimize patient management in all settings. Risk-adapted therapy on the basis molecular insights could lead to reduced intensity of therapy for many children with CNS tumors, ultimately leading to less long-term morbidity. To increase access to molecular platforms,

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 14, 2023 and published at ascopubs.org/journal/go on April 12, 2023: DOI https://doi.org/10.1200/GO.23.00017

novel strategies must be designed and implemented. For example, national or regional testing referral centers poised to evaluate pediatric CNS tumors could optimize available resources and increase their availability. Ultimately, the availability of molecular testing is not binary, and expanding testing capacity should be aligned with the clinical utility of molecular tests to inform therapeutic decision making.

In many instances, especially when complete resection is not possible, pediatric LGGs become chronic conditions. Classic cytotoxic chemotherapy rarely leads to complete remission, and multiple regimens are frequently needed. In this context, consistent access to quality-assured chemotherapy for all children with cancer is of utmost importance. Programs such as Global Platform for Access to Childhood Cancer Medicines, a collaboration of St Jude, WHO, and UNICEF, seek to guarantee the availability of quality chemotherapy for children.[13] Although targeted therapy is becoming more prevalent in the care of children with LGGs, the ideal use of these agents remains to be determined, as such drugs are unlikely to be curative and patients may need to be treated with them for many years at great financial cost.[14] Programs to increase availability, including compassionate use programs or international trials, could mitigate this barrier.[11] Additionally, the continuous updating of the WHO essential list could influence policymakers and the availability of novel drugs as their indications are more clearly defined in the coming years.

Radiotherapy is an important component of therapy for pediatric LGGs.[15] However, its ideal use remains a matter of controversy. Although tumor control with radiotherapy is superior to chemotherapy, the long-term sequalae have created hesitation around its use for pediatric patients in many settings.[16] Nonetheless, radiotherapy provided earlier in the natural history of pediatric LGGs can decrease the burden of care for families, given the shorter duration of treatment and better rate of local tumor control.[17] This would come at a possible cost, with the long-term consequences that are known from radiotherapy, but worth consideration in specific scenarios, especially where preservation of function, especially vision, is a priority. Ultimately, risk- and resource-adapted guidelines created by a multidisciplinary consensus strategy are essential to provide clinical direction.[18] To this point, the Adapted Resource and Implementation Application (ARIA) guide for LGGs, a collaboration between St Jude, the International Society of Paediatric Oncology, the Pediatric Radiation Oncology Society, the International Society of Pediatric Surgical Oncology and Childhood Cancer International, will be launched in 2023.[19] ARIA is a clinical tool that seeks to address the need for comprehensive, resource-adapted treatment recommendations for pediatric malignancies by creating evidence-based guidelines. One of the first ARIA guide will in fact be for LGG.

LGGs account for approximately a third of all cases of childhood CNS tumors.[20] Unfortunately, the global burden of pediatric LGGs is unknown, and the much-needed objective data to quantify disparities in incidence and outcomes are largely lacking. There are several reasons for this shortfall. First, quality population-based cancer registries cover <15% of pediatric patients worldwide.[2] Moreover, the largest sources on incidence and survival from population-based cancer registries have less data on pediatric CNS tumors than other pediatric malignancies, especially lacking data from LMICs.[2,4] Furthermore, in some population-based registries, morphologically benign tumors, such as pilocytic astrocytomas, are not always collected and limit the capture of LGG in these registries.[21] In addition, one of the most frequently used classification schemes by pediatric cancer registries, the International Classification of Childhood Cancer, does not segregate pediatric CNS tumors into many of the clinically relevant groups, such as LGG.[22] LGGs are mostly aggregated in the categories of astrocytomas and other gliomas and are impossible to analyze as a subgroup. Without a precise classification, it is impossible to understand the specific epidemiologic characteristics of LGGs and the track the health systems and clinical determinants associated with divergent outcomes. Finally, beyond cancer registries, only limited peer-reviewed literature exists on the outcomes of LGGs in LMICs.[23] All these factors contribute to the sparse understanding of the current burden of pediatric LGGs across the world.

Understanding the global burden of children with LGGs is essential for quantifying the disparities between incidence and survival rates in LMICs and high-income countries, identifying areas of deficiencies, and prioritizing the interventions needed to address existing disparities. These data are crucial if we are to track the impact of the GICC on outcomes and reach the 60% survival target. For this, investment in quality cancer registries and an updating of the currently used classification schemes are urgently needed.[24] Partnerships and programs to increase the capacity of population- and hospital-based cancer registries are currently underway in recognition of the complementary role each play for policy and clinical surveillance purposes.[25] Furthermore, a proposed classification scheme that creates a more clinically relevant segregation for pediatric CNS tumors is currently being developed and validated as part of the childGICR initiative.[26]

The perceived disparities in outcomes in LGGs are rooted in inequalities in access to care, as many of the elements needed for quality care for children with LGGs are not always available in LMICs.[27] Essential resources, in terms of the availability of and accessibility to infrastructure and specialists, are often scarce in resource-limited settings.[28,29] Narrowing the care gap for pediatric LGGs poses an enormous challenge, but partnerships among stakeholders can be leveraged to define a path for the future. Multisectoral and interdisciplinary partnerships and initiatives are needed to improve the outcomes of children with LGG tumors. To impact the

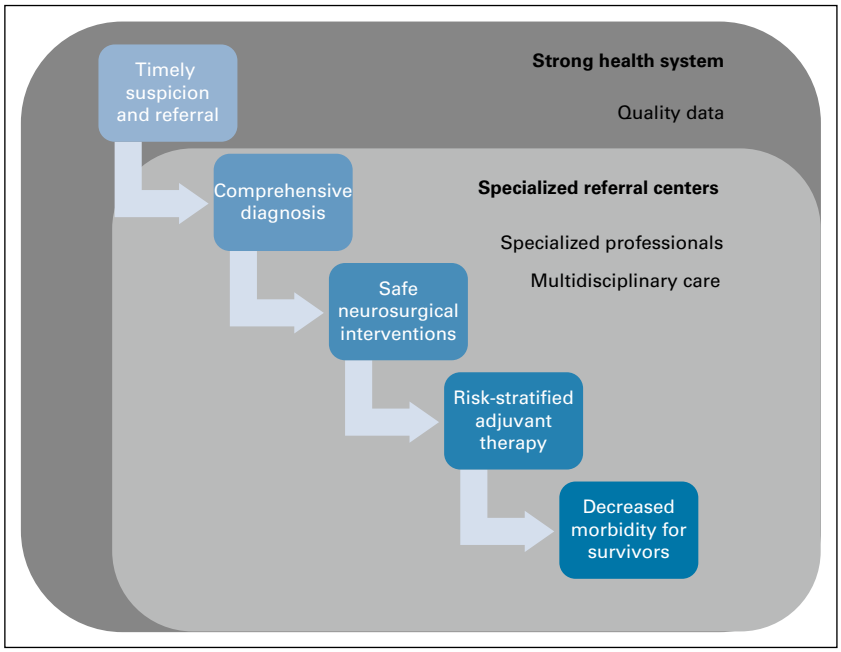

FIG 1. Path for quality care for children with LGGs. Quality care for LGG requires increasing access to diagnosis, referral to specialized centers, comprehensive multidisciplinary care, and monitoring and support for long-term survivors. LGG, low-grade glioma.

volume of patients diagnosed in a timely fashion and provide comprehensive, quality care, the entire care continuum must be considered, from symptom start to long-term survivorship (Fig 1). Under the umbrella of the WHO GICC, strategies to increase the specialized workforce are an essential component of increasing access to quality care. Furthermore, engaging health care professionals, from first-contact providers to subspecialists, will be key to allowing all children with LGGs to be diagnosed and cared for. Specific to LGG as an index cancer, and pediatric CNS tumors more broadly, engaging neurosurgeons and neurosurgical professional societies will be key to aligning GICC workstreams with existing global neurosurgical programs. Strategies to optimize existing resources, by creating centralized diagnostic or treatment centers (centers of excellence) can be leveraged to provide comprehensive care. Ultimately, high-volume specialized centers have better outcomes for pediatric CNS tumors.[30]

It is important to emphasize the relevance of pediatric LGG treatment to the wider problem of pediatric cancer. Because of the multifaceted care required to diagnose and treat LGGs, investments in improving outcomes for patients with LGGs will undoubtedly lead to enhancements in the coordination and integration of health systems, thereby benefitting the broader pediatric population. Cures should be limited only by our understanding of the biology of pediatric cancers, not by the availability of care.

AFFILIATIONS

[1]Department of Global Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN
[2]Department of Oncology, St Jude Children's Research Hospital, Memphis, TN
[3]Department of Pathology, St Jude Children's Research Hospital, Memphis, TN
[4]Department of Radiation Oncology, St Jude Children's Research Hospital, Memphis, TN

CORRESPONDING AUTHOR

Daniel C. Moreira, MD, MEd, Department of Global Pediatric Medicine, St Jude Children's Research Hospital, 262 Danny Thomas Place, MS 721, Memphis, TN 38105; e-mail: daniel.moreira@stjude.org.

SUPPORT

Supported by the American Lebanese Syrian Associated Charities (ALSAC).

AUTHOR CONTRIBUTIONS

Conception and design: Daniel C. Moreira
Provision of study materials or patients: All authors
Collection and assembly of data: Daniel C. Moreira
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Catherine G. Lam
Stock and Other Ownership Interests: PharmaJet
Consulting or Advisory Role: Sanofi, Jazz Pharmaceuticals, Servier, BTG, Shire, EUSA Pharma
Speakers' Bureau: Servier, Sanofi

Nickhill Bhakta
This author is a member of the *JCO Global Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.

Frederick A. Boop
Employment: Semmes Murphey Clinic
Travel, Accommodations, Expenses: American Board of Neurological Surgeons

Thomas E. Merchant
Honoraria: Varian Medical Systems
Travel, Accommodations, Expenses: Philips Healthcare

Amar Gajjar
Consulting or Advisory Role: Roche/Genentech, QED Therapeutics, Day One Therapeutics, Geanno Bio
Research Funding: Genentech (Inst), Kazia Therapeutics (Inst)

Ibrahim Qaddoumi
Consulting or Advisory Role: SpringWorks Therapeutics, AstraZeneca

No other potential conflicts of interest were reported.

JCO Global Oncol 9:e2300017. © 2023 by American Society of Clinical Oncology

REFERENCES

1. WHO: Global initiative for childhood cancer: An overview. https://www.who.int/publications/m/item/global-initiative-for-childhood-cancer
2. Steliarova-Foucher E, Colombet M, Ries LAG, et al: International incidence of childhood cancer, 2001-10: A population-based registry study. Lancet Oncol 18:719-731, 2017
3. Ward E, DeSantis C, Robbins A, et al: Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 64:83-103, 2014
4. Allemani C, Matsuda T, Di Carlo V, et al: Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): Analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 391:1023-1075, 2018
5. Arnautovic A, Billups C, Broniscer A, et al: Delayed diagnosis of childhood low-grade glioma: Causes, consequences, and potential solutions. Childs Nerv Syst 31:1067-1077, 2015
6. Ward ZJ, Yeh JM, Bhakta N, et al: Estimating the total incidence of global childhood cancer: A simulation-based analysis. Lancet Oncol 20:483-493, 2019
7. Rajagopal R, Moreira DC, Faughnan L, et al: An international multicenter survey reveals health care providers' knowledge gap in childhood central nervous system tumors. Eur J Pediatr 182:557-565, 2022
8. Vasquez L, Montoya J, Ugaz C, et al: ONCOPEDS: A mobile application to improve early diagnosis and timely referral in childhood cancer in a low- and middle-income country—A pilot study. Pediatr Blood Cancer 68:e28908, 2021
9. Wisoff JH, Sanford RA, Heier LA, et al: Primary neurosurgery for pediatric low-grade gliomas: A prospective multi-institutional study from the Children's Oncology Group. Neurosurgery 68:1548-1555, 2011
10. Roach JT, Qaddoumi I, Baticulon RE, et al: Pediatric neurosurgical capacity for the care of children with CNS tumors worldwide: A cross-sectional assessment. JCO Glob Oncol 9:e2200402, 2023
11. Bailey S, Davidson A, Parkes J, et al: How can genomic innovations in pediatric brain tumors transform outcomes in low- and middle-income countries? JCO Glob Oncol 8:e2200156, 2022
12. Li X, Moreira DC, Bag AK, et al: The clinical and molecular characteristics of progressive hypothalamic/optic pathway pilocytic astrocytoma. Neuro Oncol 10.1093/neuonc/noac241 [epub ahead of print on October 19, 2022]
13. WHO: Global access to chemotherapy. https://www.who.int/news/item/13-12-2021-who-and-st.-jude-to-dramatically-increase-global-access-to-childhood-cancer-medicines
14. Jones DTW, Kieran MW, Bouffet E, et al: Pediatric low-grade gliomas: Next biologically driven steps. Neuro Oncol 20:160-173, 2018
15. Merchant TE, Kun LE, Wu S, et al: Phase II trial of conformal radiation therapy for pediatric low-grade glioma. J Clin Oncol 27:3598-3604, 2009
16. Bitterman DS, MacDonald SM, Yock TI, et al: Revisiting the role of radiation therapy for pediatric low-grade glioma. J Clin Oncol 37:3335-3339, 2019
17. Tsang DS, Murphy ES, Merchant TE: Radiation therapy for optic pathway and hypothalamic low-grade gliomas in children. Int J Radiat Oncol Biol Phys 99:642-651, 2017
18. Hessissen L, Parkes J, Amayiri N, et al: SIOP PODC Adapted treatment guidelines for low grade gliomas in low and middle income settings. Pediatr Blood Cancer 64:e26737, 2017
19. Adapted Resource and Implementation Application (ARIA): ARIA Guide. aria.stjude.org
20. Ostrom QT, Price M, Ryan K, et al: CBTRUS statistical report: Pediatric brain tumor foundation childhood and adolescent primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. Neuro Oncol 24:iii1-iii38, 2022
21. Dean F, Henrikson H, Xu R, et al: Challenges in determining the global burden of low-grade pediatric brain tumors. Pediatr Blood Cancer 68:S308-S309, 2021
22. Steliarova-Foucher E, Stiller C, Lacour B, et al: International classification of childhood cancer, third edition. Cancer 103:1457-1467, 2005.103
23. Ward R, Jones HM, Witt D, et al: Outcomes of children with low-grade gliomas in low- and middle-income countries: A systematic review. JCO Glob Oncol 8:e2200199, 2022
24. Ilbawi AM, Lam CG, Ortiz R, et al: Investing in childhood cancer registries to drive progress. Lancet Child Adolesc Health 6:446-447, 2022
25. WHO: Child GICR. https://gicr.iarc.fr/childgicr
26. Moreira DC, Chen Y, Qaddoumi I, et al: EPID-05. A novel, clinically-relevant classification of pediatric CNS tumors for cancer registries using a clustering analysis. Neuro Oncol 24:i47, 2022
27. Moreira DC, Rajagopal R, Navarro-Martin Del Campo RM, et al: Bridging the gap in access to care for children with CNS tumors worldwide. JCO Glob Oncol 6:583-584, 2020
28. Atun R, Jaffray DA, Barton MB, et al: Expanding global access to radiotherapy. Lancet Oncol 16:1153-1186, 2015

29. Fleming KA, Horton S, Wilson ML, et al: The Lancet Commission on diagnostics: Transforming access to diagnostics. Lancet 398:1997-2050, 2021
30. Kramer S, Meadows AT, Pastore G, et al: Influence of place of treatment on diagnosis, treatment, and survival in three pediatric solid tumors. J Clin Oncol 2:917-923, 1984