Published in final edited form as:

Eur J Cancer. 2019 January ; 106: 171–180. doi:10.1016/j.ejca.2018.10.016.

Long-term health and social function in adult survivors of pediatric astrocytoma: A report from the Childhood Cancer Survivor Study

Karen E. Effinger, MD, MS^a, Kayla Stratton, MS^b, Paul Graham Fisher, MD^c, Kirsten K. Ness, PT, PhD^d, Kevin R. Krull, PhD^{d,e}, Kevin C. Oeffinger, MD^f, Gregory T. Armstrong, MD, MSCE^d, Leslie L. Robison, PhD^d, Melissa M. Hudson, MD^{d,e,g}, Wendy M. Leisenring, ScD^b, Paul C. Nathan, MD, MSc^h

^aDepartment of Pediatrics, Emory University, Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta, 2015 Uppergate Dr., Rm 426I, Atlanta, GA 30322 United States

^bDepartment of Clinical Research and Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N, PO Box 19024, Seattle, Washington 98109 United States

^cDepartments of Pediatrics, Neurology and Human Biology, Stanford University, 750 Welch Road, Suite 317, Palo Alto, CA 94304 United States

^dDepartment of Epidemiology and Cancer Control, 262 Danny Thomas Place, MS 735, Memphis, TN 38105 United States

^eDepartment of Psychology, 262 Danny Thomas Place, MS 735, Memphis, TN 38105 United States

^gDepartment of Oncology St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS 735, Memphis, TN 38105 United States

^fDepartment of Medicine, Duke University School of Medicine, 2424 Erwin Dr., Suite 601, Durham, NC 27705 United States

^hDepartments of Paediatrics and Heath Policy, Management, and Evaluation, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, ON M5G 1X8 Canada

Abstract

Background: Although pediatric astrocytoma has an excellent five-year survival rate, survivors remain at risk for morbidity and late mortality. This study aimed to estimate the risk of late mortality, chronic conditions, poor health status and social impairment in aging pediatric astrocytoma survivors.

Corresponding Author: Karen E. Effinger, MD, MS, 2015 Uppergate Dr., Rm 426I, Atlanta, GA 30322, Phone: 404-785-2526, Fax: 404-785-1418, karen.effinger@emory.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest Statement:
None Declared

Methods: 1,182 five-year astrocytoma survivors diagnosed between 1970–86 and 4,023 siblings enrolled in a retrospective cohort study were evaluated longitudinally. Kaplan-Meier estimates of late mortality and cumulative incidence of serious chronic conditions were estimated. Cox regression models provided hazard ratios (HR) with 95% confidence intervals (CI) for development of chronic conditions, and generalized linear models provided relative risks (RR) of poor health status and social outcomes.

Results: At 30 years from diagnosis, cumulative late mortality was 22.1% (CI 20.0–24.3%), primarily due to disease progression or recurrence. Compared with siblings, survivors were at increased risk of serious chronic conditions (HR 4.6, CI 3.8–5.5). Survivors reported higher rates of poor general health (RR 3.3, CI 2.8–3.8), poor mental health (RR 1.9, CI 1.7–2.1), functional impairment (RR 9.0, CI 7.7–10.5), and activity limitation (RR 3.6, CI 3.1–4.2) and lower rates of college graduation (RR 0.75, CI 0.69–0.82), marriage (RR 0.62, CI 0.58–0.66), employment (RR 0.75, CI 0.72–0.79), and household income \$40,000 (RR 0.68, CI 0.64–0.73). Even survivors without radiation exposure had elevated risk of chronic conditions, poor health status, and social impairment compared to siblings.

Conclusions: Survivors of pediatric astrocytoma are at high risk for long-term complications of their disease and its treatment. They require lifelong monitoring for late effects.

Keywords

astrocytoma; late effects; long-term outcomes; health status; social outcomes; pediatric

Introduction

Astrocytoma is the most common pediatric solid tumor.¹ The current five-year overall survival (OS) rate for astrocytoma is approximately 80%.¹ However, survival varies by tumor grade and location (i.e., 5-year OS: low-grade tumors >85%,² high-grade tumors <25%³). Survivors are at risk for significant late effects, including cognitive, neurologic, and sensory impairment,^{4–9} which can affect quality of life and social functioning into adulthood. Although low-grade astrocytoma therapy is typically considered less aggressive than treatment for other central nervous system (CNS) tumors, late progression or recurrence is common if gross total resection is not achieved, leading to increased late morbidity or early mortality.

Since the clinical course of astrocytomas, especially low-grade tumors, differs from other CNS tumors, assessment of the long-term functioning of these survivors is important in order to guide management of these patients. The Childhood Cancer Survivor Study (CCSS) comprises five-year survivors of pediatric cancer who were diagnosed between 1970 and 1986. During this era, OS was approximately 55–70% for children with astrocytoma¹⁰ and treatment more commonly consisted of surgery and radiation without chemotherapy. Evaluation of long-term survivors from this period can help providers understand risk factors for adverse long-term outcomes among contemporary patients. This study aimed to estimate the risk of late mortality, serious chronic conditions, poor health status and impaired social functioning in aging pediatric astrocytoma survivors.

Methods

Participants were members of the CCSS, which includes five-year survivors of cancer diagnosed before age 21 years at one of 26 North American institutions.^{11, 12} To provide a comparison group, a random sample of CCSS participants was asked to provide contact information for a full-sibling closest in age. The Institutional Review Board at each center approved the protocol and participants provided informed consent. Cancer diagnosis and treatment data were collected from the treating institutions using standardized protocols. Data for this analysis were collected from the baseline survey in 1994 and two follow-up questionnaires (Follow-up 2 in 2003, Follow-up 4 in 2007) for astrocytoma survivors and sibling controls.

Mortality and Chronic Conditions

Death records were identified using the National Death Index or from state death certificates.¹³ Questionnaires assessed demographic and health-related outcomes. A parent-proxy completed questionnaires for those deceased, <18 years, or 18 years who were unable to complete questionnaires independently. Common Terminology Criteria for Adverse Events (version 4.03) was used to grade the severity of chronic conditions on a scale of 1–5.¹⁴ Events were limited to grade 3 (severe/disabling), 4 (life-threatening), and 5 (death) conditions that had an onset prior to the time of survey completion. Conditions and age of first occurrence were self-reported; only subsequent malignant neoplasms were validated.¹¹

Health Status and Social Outcomes

Health status domains were used to document perceived health among survivors and siblings.^{15, 16} To assess general health, participants were asked, “Would you say your health is excellent, very good, good, fair, or poor?” Those with fair or poor health were classified as having poor general health. Functional impairment was assigned to those who indicated that health problems resulted in the need for help with personal care or routine tasks, or difficulty holding jobs or attending school. Activity limitation was assigned to those who indicated their ability to participate in moderate activities, climb stairs or walk one block were limited 3 months over the past two years. Poor mental health was assigned to anyone with a T-score (based on sex-specific values) of ≥63 on the 18-item Brief Symptom Inventory global severity index or one of three symptom scales.^{17, 18} Evaluation of cancer-related pain and anxiety in survivors included the questions: “Do you currently have pain as a result of your cancer or its treatment?” and “Do you currently have anxieties/fears as a result of your cancer or its treatment?” Answers of moderate, very or a lot of pain or anxieties/fears were collapsed to constitute an adverse outcome and compared with no or a small amount of pain or anxieties/fears. Social outcomes included education, employment, marital status, and household income.

Analysis

Demographic, treatment, chronic condition, health status, and social data were summarized with descriptive statistics. Cumulative mortality rates were estimated. United States age- and sex-specific mortality rates from Centers for Disease Control January 2017 data were used

to compute expected mortality based on number of deaths each year since diagnosis, and were plotted as comparative mortality curves. Cumulative mortality rates by cause of death were calculated with other causes of death treated as competing risks.¹⁹ Cumulative incidences of grade 3–5 conditions were estimated from cohort entry at age five years in siblings and five years post-cancer diagnosis in survivors and stratified based on treatment with or without radiation. Death from circumstances other than a chronic condition was treated as a competing risk event.¹⁹ Displayed curves start at the prevalence of conditions that occurred prior to cohort entry. Appendix figures display cumulative incidence conditional upon not having the pertinent condition at 0, 5 and 10 years after cohort entry. Wald tests compared differences in cumulative incidence of chronic conditions at 25 years after cohort entry. Multivariable cox regression models adjusted for sex and race were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for development of grade 3–5 conditions after cohort entry in survivors relative to siblings, with attained age as the scale. Cox models with time since diagnosis as the scale were used to determine factors associated with development of chronic conditions in survivors. When evaluating the association of treatment factors with chronic conditions, covariates with a univariable significance level of <0.1 were included in multivariable models. Chi-square tests were performed to test for differences in health status based on age group. Multivariable generalized linear models with log-link function and Poisson error distribution were employed to directly estimate relative risks (RR) of poor health status and social outcomes between survivors and siblings, and incorporated generalized estimating equations to account for within-person correlations in outcome prevalence as reported on multiple questionnaires.²⁰ Separate regression models were fit for survivors with and without radiation exposure for those with treatment data available. Because participants contributed data from one to three questionnaires, analyses used the survey as the denominator and included survey-specific covariates. RR estimates were adjusted for attained age category (<18, 18–24, 25–29, 30–34, 35–39, 40 years), sex, and race. Evaluations of health status were limited to those alive and 18 years at survey completion to limit proxy completion. Analyses were also performed adjusting for proxy status and proxy/survivor interaction to evaluate the impact of proxy completion on report of poor health status. Evaluations of social outcomes were limited to those alive and 25 years at survey completion. All p-values are two-sided utilizing a 0.05 significance level. Analyses were implemented using SAS version 9.4 (SAS Institute, Cary NC).

Results

1,841 5-year astrocytoma survivors were eligible for CCSS. 1,182 astrocytoma survivors and 4,023 siblings had baseline data with 1,073 survivors and all siblings alive at baseline survey completion; 744 survivors and 2,944 siblings were alive and completed Follow-up 2; and 612 survivors and 2,373 siblings were alive and completed Follow-up 4 (Figure A.1). Of the 796 adult survivor and 3,206 adult sibling participants alive at baseline, 3.6% and 1.8% had proxy-report, respectively. In survivors, this increased to 21.9% (163/743) and 26.8% (164/612) on the Follow-up 2 and Follow-up 4 surveys compared to 3.2% (91/2861) and 3.4% (80/2370) in siblings. Median time from diagnosis to last follow-up was 23.4 years

(range 7.3–38.9). 63% of survivors received radiation with most receiving 50Gy and 36% received no chemotherapy or radiation (Table 1).

Mortality

Among 1,841 astrocytoma survivors eligible for CCSS, there were 383 deaths. The 30-year all-cause cumulative mortality rate was 22.1% compared with 3.5% in the United States general population (Figure A.2). Cause of death was known in 327 survivors (85.0%). The most common cause of death was recurrence or progressive disease (44%) with a 30-year cumulative mortality rate of 9.6% (CI:8.2–11.0%; Figure 1). Other causes of death included: subsequent neoplasm (18.4%), other neurological conditions (7.0%), cardiac disease (5.5%), stroke (1.5%), other medical conditions (8.3%), and external causes (7.7%). Of the 1,182 CCSS participants, 142 were deceased prior to the baseline survey and 125 (11.6% alive at baseline) died during the study period.

Chronic Conditions

The prevalence of at least one grade 3–5 chronic condition in survivors was 37.1% (CI:34.3–39.8%) at cohort entry, which increased to a cumulative incidence of 56.7% (CI:53.3–60.1%) at 25 years after cohort entry, compared with 1.4% (CI:1.1–1.8%) and 8.7% (CI:7.8–9.7%) respectively in siblings. The organ systems most commonly affected in survivors by 25 years after cohort entry were neurologic (25.8% [CI:23.0–28.6%]), visual (19.3% [CI:17.0–21.7%]), and auditory (16.6% [CI:14.1–19.4%]); Tables A.1, A.2). Additionally, survivors were more likely to develop a stroke compared to siblings (12.8% [CI:10.1–15.6%] vs. 0.2% [CI:0.1–0.4%], $p<0.001$).

Survivors who received radiation had a higher cumulative incidence of chronic conditions at 25 years compared with survivors without radiation exposure (69.4% [CI:64.9%–73.3%] vs. 32.1% [CI:27.8%–39.5%], $p<0.001$; Figure 2). After adjusting for sex, race, and exposure to chemotherapy, survivors treated with cranial radiation doses <50Gy were 2.3 times (CI:1.3–4.1) and survivors exposed to cranial radiation 50Gy were 3.1 times (CI:2.1–4.7) more likely than survivors treated without cranial radiation to develop a chronic condition at equivalent times since diagnosis (Table A.3). Any chemotherapy exposure was associated with an increased risk of developing stroke (HR:2.4; CI:1.4–4.2), neurologic (HR:2.5; CI:1.4–4.4), visual (HR:3.7; CI:1.6–8.4), and cardiac (HR:5.3; CI:1.7–16.3) conditions compared to treatment without chemotherapy.

Survivors, who did not have a grade 3–5 chronic condition at cohort entry remained at risk of developing such a condition over time. In survivors with radiation exposure who did not have a condition at cohort entry, the cumulative incidence of at least one condition at 25 years was 45.2% (CI:38.6–51.6%) compared with 12.5% (CI:8.2–17.8%) in survivors without radiation exposure and 7.7% (CI:6.8–8.6%) in siblings (Figure A.3). Compared with siblings, survivors were significantly more likely to develop a new grade 3–5 condition (HR: 4.6; CI:3.8–5.5), particularly a stroke (HR:27.2; CI:15.7–27.2), auditory (HR:15.4; CI:10.6–22.4), or neurologic (HR:10.3; CI:7.2–14.7) condition (Figure 3). This remained true in survivors without radiation exposure (new chronic condition HR:1.6, CI:1.1–2.3; stroke HR: 6.0, CI:2.5–14.8; auditory HR:3.5, CI:1.7–7.3; neurologic HR:3.9, CI:2.1–7.0). Similar

results were found in sensitivity analyses limited to survivors alive at baseline (data not shown).

Health Status

Attained age was not significantly associated with report of poor health status by survivors in any of the health status domains (Table A.4). The effect of survivor status on poor health status was attenuated across all domains in models adjusted for chronic conditions (Table 2). However, compared with siblings, survivors were more likely to experience functional impairment, poor general health, activity limitations, and poor mental health, which remained true when evaluating survivors without radiation exposure. Proxy-report was associated with increased reporting of poor general health, functional impairment and activity limitations in both survivors and siblings; however, proxy-report of activity limitations was greater in survivors compared to siblings (data not shown).

Social Outcomes

Among all survivors, 40% earned a college degree or higher compared with 55% of siblings (RR:0.75; CI:0.69–0.82) and 52% were ever married compared with 85% of siblings (RR: 0.62; CI:0.58–0.66). Survivors were also less likely than siblings to be employed or have household income $\geq$ \$40,000 (Table 2). While survivors without radiation exposure were just as likely as siblings to graduate from college, they were less likely to be employed, have income $\geq$ \$40,000 or be married. Adjusting for presence of chronic conditions had little impact on the risk of poor social outcomes.

Discussion

While astrocytoma has a high five-year overall survival rate, our study found that survivors have an increased risk of premature mortality, chronic conditions, poor health status, and impaired social functioning. The majority of astrocytoma survivors developed a serious condition or had died by 25 years in the cohort. In turn, these conditions affected all domains of health status, particularly limiting daily function and activity. Survivors were less likely than siblings to earn a college degree, have a household income $\geq$ \$40,000, be employed, or get married.

Although CCSS data did not include tumor grade, given the very poor five-year survival for high-grade astrocytoma in this era, the majority of these patients were survivors of low-grade astrocytoma. In this cohort of five-year survivors, the 30-year overall cumulative mortality rate was 22.1%, which is consistent with a 30-year overall survival rate of 74.8% previously reported in pediatric low-grade gliomas.²¹ In addition to a high mortality risk, we found that the cumulative incidence of serious conditions continued to increase as survivors aged. Unfortunately, less than half of childhood cancer survivors receive risk-adapted care focused on preventing or detecting these late effects²² and many primary care providers are unaware of the risk profile of childhood cancer survivors.^{23, 24}

Risk-adapted care is particularly important in stroke prevention. From cohort entry to 25 years later, the risk of developing a stroke after cohort entry was 27-fold higher in survivors compared to siblings and nearly 44-fold higher in survivors exposed to radiation.

Additionally, this study found a 6-fold increased risk of late-onset stroke in survivors without radiation exposure, a novel finding. While neurofibromatosis-1 (NF1) status was not captured by CCSS, it is likely that a significant proportion of the survivors were affected.²⁵ NF1 is associated with cerebral vasculopathy; however, the risk of developing a stroke for patients with NF1 compared to the general population is only 20% higher.²⁶ The CCSS has reported that the combination of diabetes mellitus and hypertension increases the risk of late-occurring stroke over 14-fold.²⁷ Furthermore, it is established that survivors exposed to 50Gy of cranial radiation have a 33% 10-year cumulative incidence of late recurrent stroke with increased risk in those with hypertension.²⁸ Monitoring and management of atherosclerotic risk factors in this population is of great importance; however, guidelines for the primary prevention of stroke do not address these risk factors and primary care providers may not be aware of this risk.²⁹ More studies are needed to evaluate the risk factors associated with late-onset stroke in survivors without radiation exposure and to determine if screening with neuroimaging or initiation of aspirin prophylaxis could prevent stroke in this high-risk population.

Survivors in this study also had a 15-fold risk of developing late-onset hearing loss compared with siblings, with a 24-fold increased risk in those exposed to radiation. Radiation-induced hearing loss may develop years after completion of therapy. One study of 235 childhood cancer survivors who received cranial radiation found the median time from radiation therapy to sensorineural hearing loss onset was 3.6 years (range: 0.3–13.2) with 65% of patients continuing to have decline in hearing sensitivity on subsequent evaluations.³⁰ This may explain why we found that 12.3% of survivors with radiation exposure who did not have self-reported hearing loss at 10 years developed hearing loss by 25 years in the cohort. However, once survivors leave the pediatric oncology setting, they may no longer receive standardized hearing screening. In the general population, age-related hearing loss is associated with activity limitations, restrictions in social engagement, and emotional distress.³¹ Amplification devices may improve quality of life in these survivors if hearing loss is detected.³²

Our study also found increased risk of poor health status across all domains and impairments in social outcomes including education, employment, earning, and relationships. These findings are consistent with smaller studies of low-grade astrocytoma survivors which reported survivors had trouble with mental health, relationships, and education.^{6, 8, 33} In our study, survivors without radiation exposure were as likely to graduate from college as siblings; however, survivors were not asked about educational accommodations, so we may not have captured all learning challenges. A previous study of adult survivors of childhood cancer in Britain found that CNS tumor survivors, survivors who received any radiation and survivors with intellectual disabilities were less likely to marry compared to the general population.³⁴ Our study revealed that adult astrocytoma survivors, including those without radiation exposure, were less likely to marry and had lower earnings than siblings, two important markers of social achievement. These findings highlight the importance of psychological screening and early social interventions like vocational rehabilitation, which can help survivors reach their full potential.³⁵ Additionally, these survivors may benefit from cognitive remediation programs, group skills therapy, and pharmacologic interventions with

stimulant medications in order to decrease cognitive dysfunction and improve social milestone achievement.³⁶

When interpreting our findings, it is important to note that survivors in this study were treated between 1970–86. Since that time, there have been changes in the treatment approach to low-grade astrocytoma. Data now support subtotal resection in tumors where gross total resection may lead to significant neurologic deficits.³⁷ Chemotherapy is as an effective means to delay or avoid the need for radiation in survivors without a complete resection, leading to fewer survivors with exposure to cranial radiation.³⁷ Conformal radiotherapy techniques and use of proton radiation have decreased the volume of radiation exposure to healthy tissues. While these advances should lead to improved outcomes in astrocytoma survivors, it is important to note that survivors in this study who were not exposed to radiation were still 60% more likely to develop a chronic condition compared with siblings and were at increased risk for poor health status and social impairments. Moreover, a subset of astrocytoma survivors will continue to require cranial radiation doses 50Gy. Additionally, it is important to understand the challenges faced by survivors treated prior to contemporary advances since 17% of all of childhood CNS tumor survivors living in the United States were diagnosed before 1975.¹

There are limitations that should be considered when interpreting these results. The CCSS relies on self-reported data, which may underestimate medical conditions. We restricted the analysis to grade 3–5 conditions to minimize the potential for recall bias and misclassification. Neurocognitive outcomes and educational accommodations were not assessed in the most recent survey, which prevented analysis in this population. In addition, a proportion of survivors were deceased between the point of eligibility and study entry at the baseline survey while all siblings were alive. This may result in the sibling population being healthier. However, based on the age of eligibility and age at baseline questionnaire for the sibling cohort, we estimated the number of possible deaths between the point of eligibility and study entry to be 27 based on age, gender, and calendar year matched national mortality rates. Therefore, this effect should be minimal. Furthermore, survivors continued to develop more chronic health conditions after cohort entry compared to siblings and deceased survivors were not used in the analyses of health status or social outcomes. Also, proxy-report of health status may not be equivalent to self-report; however, after adjusting for the interaction between survivor status and proxy-report the only significant finding was in the activity limitation domain, which may be due to the fact that survivors with activity limitations are more likely to require proxy-report. Additionally, associations of increased risk based on exposure to chemotherapy and radiation may be confounded by indication since we were unable to determine if tumor progression or therapeutic exposures attributed to the development of the chronic conditions. Finally, the CCSS did not collect histologic grade, exact location of primary tumors, or NF1 status, all of which impact outcomes in astrocytoma survivors.

Conclusions

Adult pediatric astrocytoma survivors, including those who did not have radiation exposure, are at increased risk for premature mortality, serious chronic conditions, poor self-reported

health status, and social impairment. These survivors require lifelong monitoring for late effects and may benefit from psychological screening and early educational interventions. Due to the change in therapy over time, future studies are necessary to evaluate the trajectory of late effects of aging survivors of astrocytoma treated with more contemporary therapy and whether recent modifications to therapy aimed to decrease the risk of late morbidity have been effective. In particular, close attention should be paid to survivors without radiation exposure, many of whom did not receive chemotherapy. Research is needed to assess if changes in surgical techniques or early social interventions can decrease the risk for morbidity in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This work was supported by the Conquer Cancer Foundation of the American Society of Clinical Oncology Young Investigator Award (Effinger), the National Cancer Institute (CA55727, Armstrong) and the American Lebanese Syrian Associated Charities (ALSAC). No funding sources had a role in the collection, analysis, or interpretation of the data.

Role of the Funding Sources:

The study sponsors had no role in the collection, analysis, or interpretation of the data.

References

1. SEER Cancer Statistics Review, 1975–2014 [Internet]. National Cancer Institute. 2017 [cited October 2, 2017]. Available from: https://seer.cancer.gov/csr/1975_2014/.
2. Fisher PG, Tihan T, Goldthwaite PT, Wharam MD, Carson BS, Weingart JD, et al. Outcome analysis of childhood low-grade astrocytomas. *Pediatr Blood Cancer*. 2008;51(2):245–50. [PubMed: 18386785]
3. Pollack IF, Boyett JM, Yates AJ, Burger PC, Gilles FH, Davis RL, et al. The influence of central review on outcome associations in childhood malignant gliomas: results from the CCG-945 experience. *Neuro Oncol*. 2003;5(3):197–207. [PubMed: 12816726]
4. Armstrong GT, Conklin HM, Huang S, Srivastava D, Sanford R, Ellison DW, et al. Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro Oncol*. 2011;13(2):223–34. [PubMed: 21177781]
5. Benesch M, Lackner H, Sovinz P, Suppan E, Schwinger W, Eder HG, et al. Late sequela after treatment of childhood low-grade gliomas: a retrospective analysis of 69 long-term survivors treated between 1983 and 2003. *J Neurooncol*. 2006;78(2):199–205. [PubMed: 16739030]
6. Aarsen FK, Paquier PF, Reddingius RE, Streng IC, Arts WF, Evera-Preesman M, et al. Functional outcome after low-grade astrocytoma treatment in childhood. *Cancer*. 2006;106(2):396–402. [PubMed: 16353203]
7. Ris MD, Beebe DW. Neurodevelopmental outcomes of children with low-grade gliomas. *Dev Disabil Res Rev*. 2008;14(3):196–202. [PubMed: 18924158]
8. Turner CD, Chordas CA, Liptak CC, Rey-Casserly C, Delaney BL, Ullrich NJ, et al. Medical, psychological, cognitive and educational late-effects in pediatric low-grade glioma survivors treated with surgery only. *Pediatr Blood Cancer*. 2009;53(3):417–23. [PubMed: 19479971]
9. Zuzak TJ, Poretti A, Drexel B, Zehnder D, Boltshauser E, Grotzer MA. Outcome of children with low-grade cerebellar astrocytoma: long-term complications and quality of life. *Childs Nerv Syst*. 2008;24(12):1447–55. [PubMed: 18690461]

10. Stiller CA, Bunch KJ. Trends in survival for childhood cancer in Britain diagnosed 1971–85. *Br J Cancer*. 1990;62(5):806–15. [PubMed: 2173943]
11. Leisenring WM, Mertens AC, Armstrong GT, Stovall MA, Neglia JP, Lancot JQ, et al. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009;27(14):2319–27. [PubMed: 19364957]
12. Robison LL, Armstrong GT, Boice JD, Chow EJ, Davies SM, Donaldson SS, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. *J Clin Oncol*. 2009;27(14):2308–18. [PubMed: 19364948]
13. Armstrong GT, Chen Y, Yasui Y, Leisenring W, Gibson TM, Mertens AC, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. *N Engl J Med*. 2016;374(9):833–42. [PubMed: 26761625]
14. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355(15):1572–82. [PubMed: 17035650]
15. Hudson MM, Mertens AC, Yasui Y, Hobbie W, Chen H, Gurney JG, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA*. 2003;290(12):1583–92. [PubMed: 14506117]
16. Hudson MM, Oeffinger KC, Jones K, Brinkman TM, Krull KR, Mulrooney DA, et al. Age-Dependent Changes in Health Status in the Childhood Cancer Survivor Cohort. *J Clin Oncol*. 2014.
17. Derogatis L Brief symptom inventory (BSI) 18: Administration, Scoring, and Procedures Manual. Minneapolis, MN: National Computer Systems; 2000.
18. Zabora J, BrintzenhofeSzoc K, Jacobsen P, Curbow B, Piantadosi S, Hooker C, et al. A new psychosocial screening instrument for use with cancer patients. *Psychosomatics*. 2001;42(3):241–6. [PubMed: 11351113]
19. RJ G A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *Annals of Statistics*. 1988;16:1141–54.
20. Zou G A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702–6. [PubMed: 15033648]
21. Bandopadhyay P, Berghthold G, London WB, Goumnerova LC, Morales La Madrid A, Marcus KJ, et al. Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. *Pediatr Blood Cancer*. 2014;61(7):1173–9. [PubMed: 24482038]
22. Casillas J, Oeffinger KC, Hudson MM, Greenberg ML, Yeazel MW, Ness KK, et al. Identifying Predictors of Longitudinal Decline in the Level of Medical Care Received by Adult Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. *Health Serv Res*. 2015;50(4):1021–42. [PubMed: 25600956]
23. Nathan PC, Daugherty CK, Wroblewski KE, Kigin ML, Stewart TV, Hlubocky FJ, et al. Family physician preferences and knowledge gaps regarding the care of adolescent and young adult survivors of childhood cancer. *J Cancer Surviv*. 2013;7(3):275–82. [PubMed: 23471729]
24. Iyer NS, Mitchell HR, Zheng DJ, Ross WL, Kadan-Lottick NS. Experiences with the survivorship care plan in primary care providers of childhood cancer survivors: a mixed methods approach. *Support Care Cancer*. 2017;25(5):1547–55. [PubMed: 28050709]
25. Gutmann DH, Rasmussen SA, Wolkenstein P, MacCollin MM, Guha A, Inskip PD, et al. Gliomas presenting after age 10 in individuals with neurofibromatosis type 1 (NF1). *Neurology*. 2002;59(5):759–61. [PubMed: 12221173]
26. Terry AR, Jordan JT, Schwamm L, Plotkin SR. Increased Risk of Cerebrovascular Disease Among Patients With Neurofibromatosis Type 1: Population-Based Approach. *Stroke*. 2016;47(1):60–5. [PubMed: 26645253]
27. Mueller S, Fullerton HJ, Stratton K, Leisenring W, Weathers RE, Stovall M, et al. Radiation, atherosclerotic risk factors, and stroke risk in survivors of pediatric cancer: a report from the Childhood Cancer Survivor Study. *Int J Radiat Oncol Biol Phys*. 2013;86(4):649–55. [PubMed: 23680033]

28. Fullerton HJ, Stratton K, Mueller S, Leisenring WW, Armstrong GT, Weathers RE, et al. Recurrent stroke in childhood cancer survivors. *Neurology*. 2015;85(12):1056–64. [PubMed: 26311747]
29. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(12):3754–832. [PubMed: 25355838]
30. Bass JK, Hua CH, Huang J, Onar-Thomas A, Ness KK, Jones S, et al. Hearing Loss in Patients Who Received Cranial Radiation Therapy for Childhood Cancer. *J Clin Oncol*. 2016;34(11):1248–55. [PubMed: 26811531]
31. Gopinath B, Hickson L, Schneider J, McMahon CM, Burlutsky G, Leeder SR, et al. Hearing-impaired adults are at increased risk of experiencing emotional distress and social engagement restrictions five years later. *Age Ageing*. 2012;41(5):618–23. [PubMed: 22591986]
32. Ferguson MA, Kitterick PT, Chong LY, Edmondson-Jones M, Barker F, Hoare DJ. Hearing aids for mild to moderate hearing loss in adults. *Cochrane Database Syst Rev*. 2017;9:CD012023. [PubMed: 28944461]
33. Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. *J Clin Oncol*. 2009;27(22):3691–7. [PubMed: 19581535]
34. Frobisher C, Lancashire ER, Winter DL, Jenkinson HC, Hawkins MM, British Childhood Cancer Survivor S. Long-term population-based marriage rates among adult survivors of childhood cancer in Britain. *Int J Cancer*. 2007;121(4):846–55. [PubMed: 17450524]
35. Rusbridge SL, Walmsley NC, Griffiths SB, Wilford PA, Rees JH. Predicting outcomes of vocational rehabilitation in patients with brain tumours. *Psychooncology*. 2013;22(8):1907–11. [PubMed: 23355502]
36. Castellino SM, Ullrich NJ, Whelen MJ, Lange BJ. Developing interventions for cancer-related cognitive dysfunction in childhood cancer survivors. *J Natl Cancer Inst*. 2014;106(8).
37. Pollack IF. Multidisciplinary management of childhood brain tumors: a review of outcomes, recent advances, and challenges. *J Neurosurg Pediatr*. 2011;8(2):135–48. [PubMed: 21806354]

- At 30 years after diagnosis of astrocytoma, cumulative late mortality was 22.1%.
- 56.7% of survivors had a serious chronic condition by 30 years after diagnosis.
- Survivors reported more functional impairment & activity limitations than siblings.
- Survivors were less likely than siblings to be college educated, working or married.
- Survivors treated without radiation had increased medical & psychosocial conditions.

Figure 1.
Cause-specific cumulative mortality in five-year astrocytoma survivors (color)

Figure 2.
Cumulative incidence with 95% confidence intervals of grade 3–5 chronic health conditions in five-year survivors of astrocytoma by radiation exposure (color)

Figure 3.

Hazard ratios (HR) and 95% confidence intervals (CI) for development of grade 3–5 chronic conditions in 5-year astrocytoma survivors compared to sibling controls. Cox regression models compare survivor versus sibling risks adjusted for sex and race and accounting for age in the time scale. Asterisk marks where the confidence interval extends to 76.7.

Abbreviations: XRT, radiation exposure

Table 1:

Characteristics of five-year astrocytoma survivors and siblings

	Survivors (n=1182) N (%)	Siblings (n=4023) N (%)
Sex		
Male	632 (53.5)	1937 (48.2)
Female	550 (46.5)	2086 (51.9)
Race/Ethnicity		
White, non-Hispanic	1034 (87.7)	3509 (90.4)
Other	145 (12.3)	373 (9.6)
Unknown	3	141
Age at Last Follow-Up (years)		
<18	76 (6.4)	233 (5.8)
18–24	200 (16.9)	539 (13.4)
25–29	250 (21.2)	652 (16.2)
30–34	241 (20.4)	667 (16.6)
35–39	205 (17.3)	718 (17.9)
40	210 (17.8)	1214 (30.2)
College Degree^a		
Yes	329 (39.6)	1792 (55.4)
No	501 (60.4)	1442 (44.6)
Employed at Last Follow-up^a		
Yes	509 (62.7)	2731 (84.3)
No	303 (37.3)	510 (15.7)
Income \$40,000/year at Last Follow-up^a		
Yes	349 (51.6)	2352 (78.4)
No	328 (48.5)	650 (21.7)
Ever Married^a		
Yes	400 (52.6)	2693 (85.4)
No	361 (47.4)	461 (14.6)
Age at Diagnosis (years)		
0–4	430 (36.4)	
5–9	330 (27.9)	
10–20	422 (35.7)	
Treatment^b		
No chemotherapy or radiation	375 (35.9)	
Chemotherapy without radiation	17 (1.6)	
Radiation without chemotherapy	454 (43.5)	
Chemotherapy plus radiation	200 (19.1)	
Radiation Therapy^b		
Yes	654 (62.5)	

	Survivors (n=1182) N (%)	Siblings (n=4023) N (%)
No	393 (37.5)	
Maximal Cranial Radiation Dose^b		
None	436 (45.9)	
<50 Gray	106 (9.8)	
50 Gray	452 (44.3)	
Unknown dose	4	
Time Period of Diagnosis		
1970–1975	273 (25.5)	
1976–1980	307 (28.7)	
1981–1986	490 (45.8)	

^a Social outcomes limited to survivors and siblings alive at baseline survey and 25 years

^b Percentages calculated for survivors who provided release for medical record abstraction for treatment data

Risk ratios and 95% confidence intervals for poor health status and social outcomes in adult survivors of pediatric astrocytoma compared to siblings with and without adjustment for presence of chronic conditions^a

Table 2:

	All Survivors		Survivors: Radiation Exposure		Survivors: No Radiation	
	RR (95% CI)	aRR (95% CI) ^b	RR (95% CI)	aRR (95% CI) ^b	RR (95% CI)	aRR (95% CI) ^b
Domains of Health Status						
Poor General Health	3.3 (2.8–3.8)	2.3 (1.9–2.7)	4.1 (3.5–4.9)	2.6 (2.1–3.3)	1.9 (1.4–2.5)	1.5 (1.1–2.0)
Poor Mental Health	1.9 (1.7–2.1)	1.6 (1.4–1.8)	2.1 (1.8–2.4)	1.7 (1.4–2.0)	1.7 (1.4–2.1)	1.6 (1.3–1.9)
Functional Impairment	9.0 (7.7–10.5)	5.3 (4.4–6.4)	11.6 (9.9–13.6)	6.4 (5.2–7.9)	4.8 (3.8–6.0)	3.4 (2.6–4.3)
Activity Limitation	3.6 (3.1–4.2)	1.9 (1.6–2.3)	4.6 (3.9–5.5)	2.2 (1.9–2.7)	2.0 (1.5–2.6)	1.4 (1.0–1.8)
Social Outcomes						
College Degree	0.75 (0.69–0.82)	0.77 (0.70–0.84)	0.63 (0.55–0.72)	0.63 (0.55–0.73)	1.01 (0.90–1.1)	1.01 (0.90–1.1)
Ever Married	0.62 (0.58–0.66)	0.64 (0.60–0.69)	0.48 (0.43–0.54)	0.50 (0.44–0.56)	0.81 (0.75–0.88)	0.82 (0.76–0.88)
Current Income >\$40,000	0.68 (0.64–0.73)	0.71 (0.66–0.76)	0.58 (0.52–0.65)	0.60 (0.54–0.67)	0.87 (0.81–0.95)	0.89 (0.82–0.96)
Currently Employed	0.75 (0.72–0.79)	0.80 (0.77–0.84)	0.68 (0.63–0.72)	0.72 (0.67–0.77)	0.89 (0.85–0.94)	0.91 (0.86–0.96)

Abbreviations: RR=risk ratio; CI=confidence interval

^aHealth status models limited to alive participants 18 years of age at survey completion. Social outcome models limited to alive participants 25 years of age at survey completion. Baseline models adjusted for attained age category, sex, and race

^bComplete models adjusted for attained age category, sex, race, and presence of chronic conditions