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Original Research

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

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KEYWORDS
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Abstract ***Background:*** Although paediatric astrocytoma has an excellent 5-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 ageing paediatric astrocytoma survivors.
Methods: We longitudinally evaluated 1182 5-year astrocytoma survivors diagnosed between 1970 and 1986 and 4023 siblings enrolled in a retrospective cohort study. Kaplan–Meier estimates of late mortality and cumulative incidence of serious chronic conditions were estimated. Cox regression models provided hazard ratios (HRs) with 95% confidence intervals (CIs) for development of chronic conditions, and generalised linear models provided relative risks (RRs) of the 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 with siblings.
Conclusions: Survivors of paediatric astrocytoma are at high risk for long-term complications of their disease and its treatment. They require lifelong monitoring for late effects.

1. Introduction

Astrocytoma is the most common paediatric solid tumour [1]. The current 5-year overall survival (OS) rate for astrocytoma is approximately 80% [1]. However, survival varies by the tumour grade and location (i.e., 5-year OS: low-grade tumours >85% [2] and high-grade tumours <25% [3]). Survivors are at risk for significant late effects, including cognitive, neurologic and sensory impairment [4–9], which can affect their 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) tumours, late progression or recurrence is common if gross total resection is not achieved, leading to increased late morbidity or early mortality.

Because the clinical course of astrocytomas, especially low-grade tumours, differs from other CNS tumours, assessment of the long-term functioning of these survivors is important to guide management of these patients. The Childhood Cancer Survivor Study (CCSS) comprises 5-year survivors of paediatric cancer who were diagnosed between 1970 and 1986. During this era, OS was approximately 55–70% for children with astrocytoma [10], 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 ageing paediatric astrocytoma survivors.

2. Methods

Participants were members of the CCSS, which includes 5-year survivors of cancer diagnosed before the age of 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 centre approved the protocol, and the participants provided informed consent. Cancer diagnosis and treatment data were collected from the treating institutions using standardised protocols. Data for this analysis were collected from the baseline survey in 1994 and two follow-up questionnaires (follow-up 2 in 2003 and follow-up 4 in 2007) for astrocytoma survivors and sibling controls.

2.1. 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 I–V [14]. Events were limited to grade III (severe/disabling), IV (life threatening) and V (death) conditions that had an onset before the time of survey completion. Conditions and age of the first occurrence were self-reported; only subsequent malignant neoplasms were validated [11].

2.2. 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 that their ability to participate in moderate activities, climb stairs or walk one block were limited $\geq$3 months over the past 2 years. Poor mental health was assigned to anyone with a T-score (based on gender-specific values) of $\geq$63 on the 18-item Brief Symptom Inventory global severity index or one of the three symptom scales [17,18]. Evaluation of cancer-related pain and anxiety in survivors included the following 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.

2.3. Analysis

Demographic, treatment, chronic condition, health status and social data were summarised with descriptive statistics. Cumulative mortality rates were estimated. The United States age- and gender-specific mortality rates from the Centers for Disease Control January 2017 data were used to compute expected mortality based on the 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 III–V conditions were estimated from cohort entry at the age of 5 years in siblings and 5 years after 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 before cohort entry. Appendix figures display cumulative incidence conditional on 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 gender and race were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for development of grade III–V 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 $<$0.1 were included in multivariable models. Chi-square tests were performed to test for differences in the health status based on the age group. Multivariable generalised linear models with log-link function and Poisson error distribution were used to directly estimate relative risks (RR) of the poor health status and social outcomes between survivors and siblings and incorporated generalised estimating equations to account for within-person correlations in outcome prevalence as reported on multiple questionnaires [20]. Separate regression models were fit for survivors with and without radiation exposure for those with treatment data available. Because participants contributed data from one to three questionnaires, analyses used the survey as the denominator and included survey-specific covariates. RR estimates were adjusted for the attained age category ($<$18, 18–24, 25–29, 30–34, 35–39 and $\geq$40 years), gender and race. Evaluations of the health status were limited to those alive and $\geq$18 years at survey completion to limit proxy completion. Analyses were also performed adjusting for the proxy status and proxy/survivor interaction to evaluate the impact of proxy completion on report of the poor health status. Evaluations of social outcomes were limited to those alive and $\geq$25 years at survey completion. All p-values are two-sided using a 0.05 significance level. Analyses were implemented using SAS, version 9.4 (SAS Institute, Cary NC).

3. Results

One thousand eight hundred forty-one 5-year astrocytoma survivors were eligible for the CCSS. One thousand one hundred eighty-two astrocytoma survivors and 4023 siblings had baseline data with 1073 survivors and all siblings alive at the baseline survey completion; 744 survivors and 2944 siblings were alive and completed follow-up 2 and 612 survivors and 2373 siblings were alive and completed follow-up 4 (Fig. A1). Of the 796 adult survivor and 3206 adult sibling participants alive at the baseline survey, 3.6% and 1.8% had proxy report, respectively. In survivors, this increased to 21.9% (163/

Table 1
Characteristics of 5-year astrocytoma survivors and siblings.

Characteristics	Survivors (n = 1182) N (%)	Siblings (n = 4023) N (%)
Gender		
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 the 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 the last follow-up[a]		
Yes	509 (62.7)	2731 (84.3)
No	303 (37.3)	510 (15.7)
Income ≥$40,000/year at the 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)	
No	393 (37.5)	
Maximal cranial radiation dose[b]		
None	436 (45.9)	
50 Gy	106 (9.8)	
≥50 Gy	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 the baseline survey and ≥25 years.
[b] Percentages calculated for survivors who provided release for medical record abstraction for treatment data.

743) and 26.8% (164/612) on the follow-up 2 and follow-up 4 surveys compared with 3.2% (91/2861) and 3.4% (80/2370) in siblings. Median time from diagnosis to the last follow-up was 23.4 years (range 7.3–38.9). Sixty-three percent of survivors received radiation with most receiving ≥50Gy and 36% received no chemotherapy or radiation (Table 1).

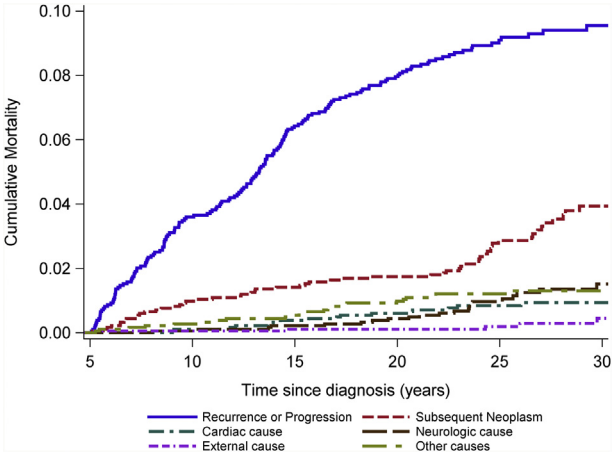

Fig. 1. Cause-specific cumulative mortality in 5-year astrocytoma survivors (colour).

3.1. Mortality

Among 1841 astrocytoma survivors eligible for the 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 (Fig. A2). The 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%; Fig. 1). Other causes of death included the following: 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 1182 CCSS participants, 142 were deceased before the baseline survey and 125 (11.6% alive at the baseline) died during the study period.

3.2. Chronic conditions

The prevalence of at least one grade III–V 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 A1 and A2). Additionally, survivors were more likely to develop a stroke compared with 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%], $p < 0.001$; Fig. 2). After adjusting for gender,

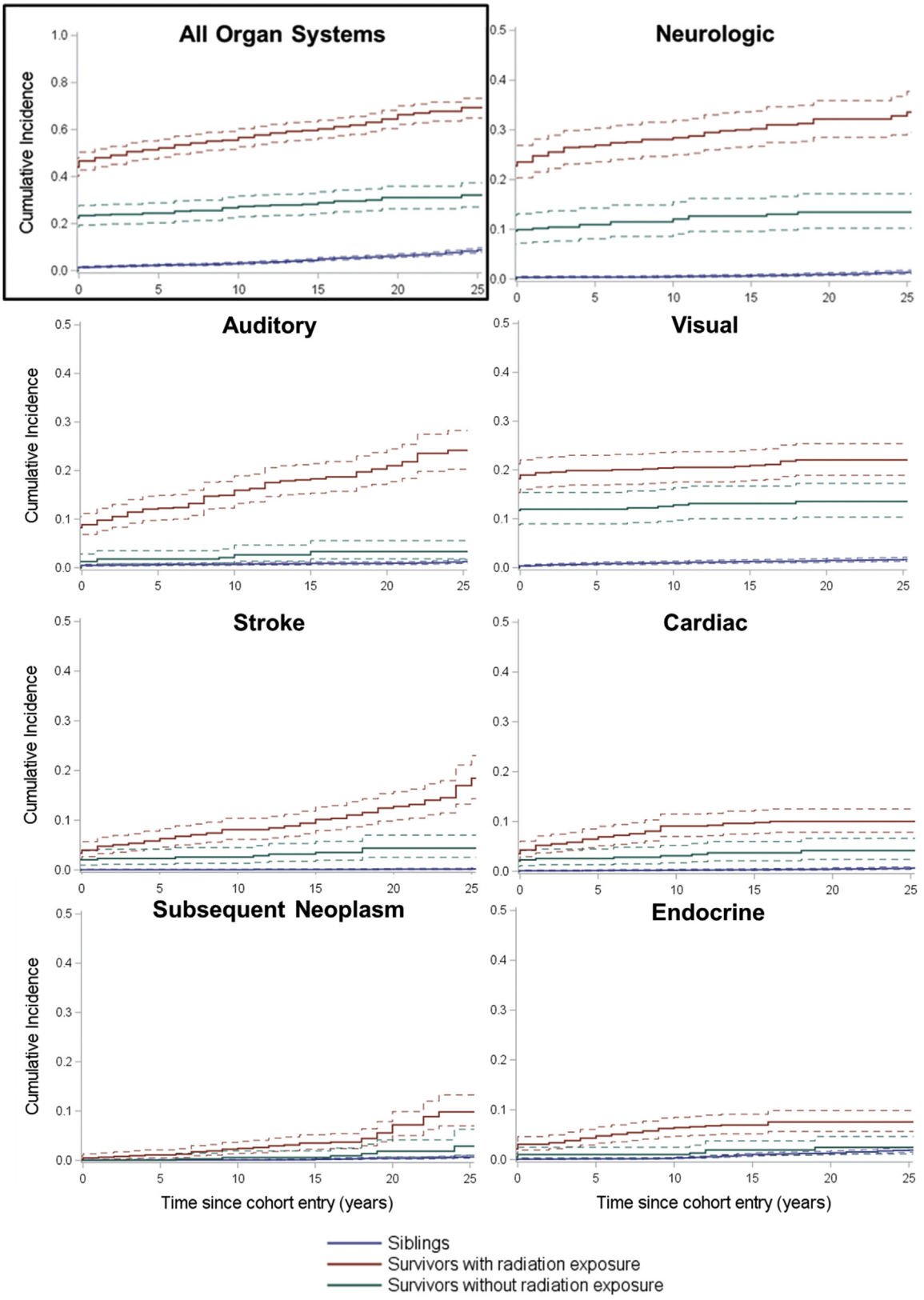

Fig. 2. Cumulative incidence with 95% confidence intervals of grade III–V chronic health conditions in 5-year survivors of astrocytoma by radiation exposure (colour).

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 A3). 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 with treatment without chemotherapy.

Survivors who did not have a grade III–V 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 (Fig. A3). Compared with siblings, survivors were significantly more likely to develop a new grade III–V 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 (Fig. 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 and neurologic HR: 3.9, CI: 2.1–7.0). Similar results were found in sensitivity analyses limited to survivors alive at the baseline (data not shown).

3.3. Health status

Attained age was not significantly associated with report of the poor health status by survivors in any of the health status domains (Table A.4). The effect of survivor status on the 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 with siblings (data not shown).

3.4. 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 ≥$40,000 (Table 2). While survivors

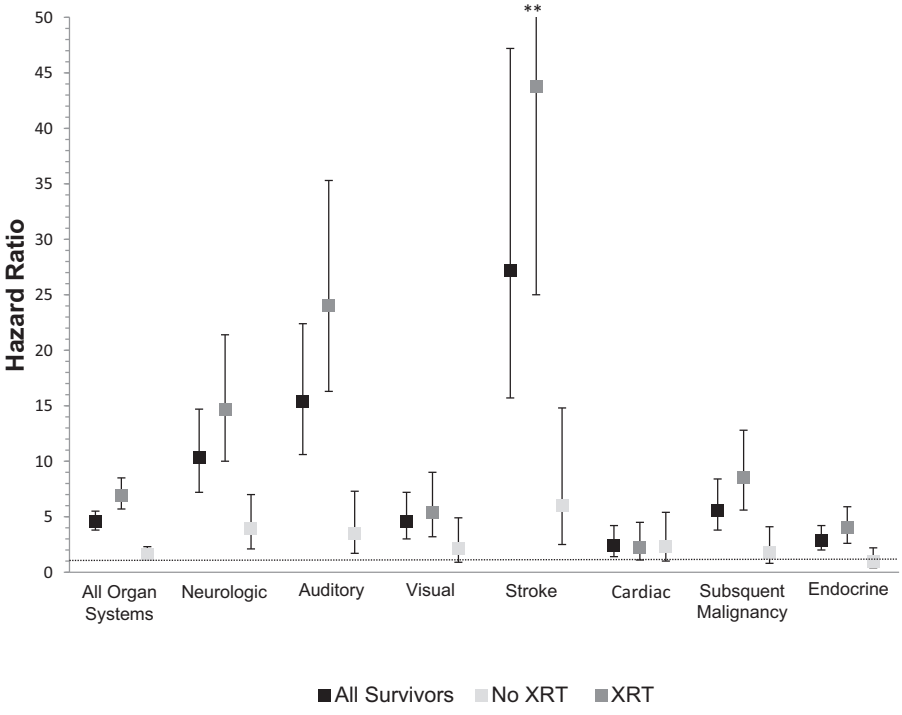

Fig. 3. Hazard ratios and 95% confidence intervals for development of grade III–V chronic conditions in 5-year astrocytoma survivors compared with sibling controls. Cox regression models compare survivor versus sibling risks adjusted for gender and race and accounting for age in the time scale. Asterisk marks where the confidence interval extends to 76.7. XRT, radiation exposure.

Table 2
Risk ratios and 95% confidence intervals for the poor health status and social outcomes in adult survivors of paediatric astrocytoma compared with siblings with and without adjustment for presence of chronic conditions.[a]

Outcomes	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 domains						
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)

RR, relative risk; aRR, adjusted relative risk; CI, confidence interval.
[a] Health 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, gender and race.
[b] Complete models adjusted for attained age category, gender, race and presence of chronic conditions.

without radiation exposure were just as likely as siblings to graduate from college, they were less likely to be employed, have income ≥$40,000 or be married. Adjusting for presence of chronic conditions had little impact on the risk of poor social outcomes.

4. Discussion

While astrocytoma has a high 5-year OS rate, our study found that survivors have an increased risk of premature mortality, chronic conditions, poor health status and impaired social functioning. Most astrocytoma survivors developed a serious condition or had died by 25 years in the cohort. In turn, these conditions affected all domains of the health status, particularly limiting daily function and activity. Survivors were less likely than siblings to earn a college degree, have a household income ≥$40,000, be employed or get married.

Although CCSS data did not include the tumour grade, given the very poor 5-year survival for high-grade astrocytoma in this era, the majority of these patients were survivors of low-grade astrocytoma. In this cohort of 5-year survivors, the 30-year overall cumulative mortality rate was 22.1%, which is consistent with a 30-year OS rate of 74.8% previously reported in paediatric 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 focussed on preventing or detecting these late effects [22], 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 with siblings and nearly 44-fold higher in survivors exposed to radiation. Additionally, this study found a sixfold increased risk of late-onset stroke in survivors without radiation exposure, a novel finding. While the neurofibromatosis-1 (NF1) status was not captured by the 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 with 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 that 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 paediatric oncology setting, they may no longer receive standardised 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 the quality of life in these survivors if hearing loss is detected [32].

Our study also found increased risk of the 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 that 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 tumour survivors, survivors who received any radiation and survivors with intellectual disabilities were less likely to marry compared with 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 such as vocational rehabilitation, which can help survivors reach their full potential [35]. Additionally, these survivors may benefit from cognitive remediation programmes, group skills therapy and pharmacologic interventions with stimulant medications 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 and 1986. Since that time, there have been changes in the treatment approach to low-grade astrocytoma. Data now support subtotal resection in tumours 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 the poor health status and social impairments. Moreover, a subset of astrocytoma survivors will continue to require cranial radiation doses $\geq$50Gy. Additionally, it is important to understand the challenges faced by survivors treated before contemporary advances because 17% of all of childhood CNS tumour 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 III–V conditions to minimise 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 that 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 with siblings, and deceased survivors were not used in the analyses of the health status or social outcomes. Also, proxy report of the health status may not be equivalent to self-report; however, after adjusting for the interaction between the 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 because we were unable to determine if tumour progression or therapeutic exposures attributed to the development of the chronic conditions. Finally, the CCSS did not collect the histologic grade, exact location of primary tumours or NF1 status, all of which impact outcomes in astrocytoma survivors.

5. Conclusions

Adult paediatric 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. Owing to the change in therapy over time, future studies are necessary to evaluate the trajectory of late effects of ageing 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.

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

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.10.016.

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