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Treatment and Outcomes for Central Nervous System Tumors in Australian Adolescents and Young Adults: A Population-Based National Study

Rosemary Harrup, MBBS, FRACP, FRCPA,[1] Victoria M. White, PhD,[2,3] Michael Coory, MBBS, PhD,[4] Rick Walker, MBBS, FRACP,[5–7] Antoinette Anazodo, MBBS, PhD, FRACP,[8–10] Gemma Skaczkowski, PhD,[3,11] Helen Bibby, MPsych,[3] Michael Osborn, MBBS,[12,13] Marianne B. Phillips, MBCHB, FRCP, FRACP,[14] Rachel Conyers, MBBS, PhD, FRACP,[15] Kate Thompson, MSW,[16] Lisa M. Orme, MBBS,[15] Ross Pinkerton, MD,[17] and Wayne Nicholls, MBBS, FRACP[5,7]

Purpose: While central nervous system (CNS) tumors account for only 10% of adolescent and young adult (AYA) cancers, they are the leading cause of cancer death in this age group. Using national data for Australia, we describe the presentation, treatment, and survival for AYAs diagnosed with CNS tumors.
Methods: A population-based study of 15–24 year-olds diagnosed with CNS tumors (low- and high-grade glioma [LGG, HGG], medulloblastoma [MB], primitive neuroectodermal tumors [PNET], ependymoma [EP]) or other (e.g., low-grade neuronal tumor) between 2007 and 2012. Clinical details were extracted from hospital medical records for each patient. Treatment centers were classified as pediatric or adult services.
Results: Two hundred seventy-five patients (129 LGG, 77 HGG, 23 MB, 10 PNET, 19 EP, 17 other) were identified, with 17% treated at pediatric hospitals. Symptoms (headache [53%], nausea [31%]) were present for a median of 3 weeks before consulting a health professional. Of LGG patients, 15% had radiotherapy (RT) and 12% chemotherapy (CT). Of HGG patients, 81% had RT and 75% CT. All MB and PNET were managed with surgery, and 74% of MB and 80% of PNET had both RT and CT. Treatment did not differ by treatment center type. Five-year survival for LGG and EP was over 80%, but was 42% for HGG and 20% for PNET.
Conclusions: This national, population-based study indicates similar treatment for AYA patients with CNS tumors between pediatric and adult services. Poor outcomes for HGG and PNET patients highlight the need for clinical trials of novel approaches for these tumors.

Keywords: adolescents and young adults, CNS tumors, brain tumors, population-based, treatment, survival

[1]Medical Oncology/Haematology, Royal Hobart Hospital, Tasmania, Australia.
[2]School of Psychology, Deakin University, Victoria, Australia.
[3]Centre for Behavioural Research in Cancer, Cancer Council Victoria, Victoria, Australia.
[4]Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Victoria, Australia.
[5]Oncology Services Group, Queensland Children's Hospital, Queensland, Australia.
[6]Oncology Unit, Princess Alexandra Hospital, Queensland, Australia.
[7]School of Medicine, University of Queensland, Queensland, Australia.
[8]Kids Cancer Centre, Sydney Children's Hospital, New South Wales, Australia.
[9]Nelune Comprehensive Cancer Centre, Prince of Wales Hospital, New South Wales, Australia.
[10]School of Women's and Children's Health, University of New South Wales, Australia.
[11]Department of Rural Health, Allied Health and Human Performance, University of South Australia, Australia.
[12]Youth Cancer Service, Royal Adelaide Hospital, South Australia, Australia.
[13]Department of Haematology and Oncology, Women's and Children's Hospital, South Australia, Australia.
[14]Oncology, Haematology & Bone Marrow Transplantation, Perth Children's Hospital, Perth, Western Australia, Australia.
[15]Children's Cancer Centre, The Royal Children's Hospital, Victoria, Australia.
[16]Victorian Adolescent & Young Adult Cancer Service, Peter MacCallum Cancer Centre, Victoria, Australia.
[17]Hummingbird House Children's Hospice, Brisbane, Australia.

Introduction

Ten percent of adolescent and young adult (AYA) cancers involve the central nervous system (CNS). While survival for AYAs with solid tumors, including CNS, improved in the 1970s and 1980s, improvements in more recent decades have lagged behind those for adult and pediatric populations.[1,2] Between 2003 and 2007, cancer was the most common cause of nonaccidental death for Australian AYAs, with CNS cancer the leading cause of cancer death.[3]

Over 100 different tumor types are classified as CNS tumors with these located in the brain or spinal cord. While gliomas are the most common type of malignant CNS tumor at all ages, the incidence of other subtypes differ by age, with for example, medulloblastoma (MB) and ependymoma (EP) more common in children than adults.[4] AYAs experience both pediatric and adult CNS tumors, with low-grade glioma (LGG), high-grade glioma (HGG), and MB the most common in this age group.[4,5] While the role of radiotherapy (RT) and chemotherapy (CT) in the management of these tumors depends on subtype, grade, and extent of residual tumor, age (e.g., pediatric or adult) can also play a role[4] with for example RT standard care for adults with LGG[4] and those with residual tumor, but is not considered standard for children with LGG. With little evidence directing whether treatment for AYA CNS tumor should follow adult or pediatric standards, treatment may depend in part on the type of hospital attended (adult or pediatric).[6,7]

There is little information on the treatment of AYA CNS cancers at the population level. A previous Australian study, including 60 AYAs age 16 to 24 years with brain tumors diagnosed between 1992 and 1996 found that only two patients were enrolled in a clinical trial although few other treatment details were reported.[8] A study from the United Kingdom examining management of 163 AYA brain tumors diagnosed between 1990 and 2009 in Yorkshire found care variations by specialty of coordinating clinician (e.g., pediatrician, neurosurgeon, oncologist).[9] A recent study from the United States of 63 astroblastoma tumors in patients 0–39 years of age found that RT and CT were used more often for high-grade tumors.[10] Impact of treatment location (e.g., pediatric vs. adult setting) was not explored. Other studies describing treatment of CNS tumors in AYAs have focused on care delivered at one clinic,[11–14] which limits their generalizability to the population level.

This is the first study to use population-based data for 15–24-year-old Australians diagnosed with CNS tumors to document nationwide patterns of care. We report time-to-diagnosis, initial symptoms, first contact with health system, type of facility for upfront treatment, and treatments received. This age range matches the definition of AYA for Australian cancer services, which are located at both pediatric (generally 0–17 years) and adult hospitals. Each year around 60 AYAs are diagnosed with CNS tumors across Australia, making these cancers relatively rare. Given the lack of definitive recommendations regarding the optimal treatment protocol for AYAs with different CNS tumors, we also examine whether treatment location (pediatric or adult hospital) influences treatment.

Methods

Patients

Patients 15–24 years of age, diagnosed with brain or CNS cancer (ICD: C70–72), between January 1, 2007 and December 31, 2012 in the six states of Australia were eligible. Eligible diagnoses were LGG, HGG, MB, primitive neuroectodermal tumors (PNET), EP, or other (e.g., low-grade neuronal tumor, choroid plexus papilloma) accounting for ~92% of CNS tumors in Australian AYAs over the study period.[2,3] Germ cell tumors and CNS lymphomas were not eligible. As patients in this study were diagnosed before the 2016 World Health Organization CNS classification review, we retained the PNET classification.

Procedure

Study procedures have been described previously.[15] In brief, all cancers in Australia must be reported to state-based population cancer registries (CaR), recording age, gender, residential location, and cancer type. Details of staging and treatment are not recorded. Eligible patients were identified from four of the six CaR. The fifth CaR provided a list of hospitals and the number of eligible patients each notified to the CaR during the study period. Software and hardware upgrades within the final CaR prevented external data requests from being processed. In this state, leading AYA clinicians identified eligible cases from hospital-based medical records.

Data were collected retrospectively from patient medical records at treating hospitals. The study had ethics approval from each state's lead Institutional Ethics Review Body and local institutional governance as required. Data were collected on 92% of cases identified as eligible from the four CaRs.

Data extracted

Information extracted from each individual's medical record included: type and duration of initial symptom(s), type of health professional first consulted, referral, date of diagnosis, diagnostic procedures, disease location, size (largest dimension reported), disease extent and grade, treatment (i.e., surgery, RT, and CT), presentation at multidisciplinary team (MDT) meetings, clinical trial enrolment, and date of progression or death. Treatment setting (pediatric vs. adult) was determined for initial treatment location. Age at diagnosis and gender were extracted from the medical record or CaR. Date of death was obtained from the National Death Index.

Survival data

Survival was calculated by data linkage to the National Death Index using sex, date of birth, and address.

Statistical analyzes

Descriptive statistics characterized the sample. Diagnostic data were examined by tumor type (high and LGG distinguished) with chi-square analyzes examining differences. Treatment data examined by tumor type, with chi-square analyzes examining association between treatment and type of hospital (adult or pediatric). Survival analyzes were conducted using October 1, 2016 as the censor date. Relapse-free survival (RFS) was calculated using date of relapse as recorded in medical records or death as the outcome. The cumulative overall survival (OS) and RFS estimates at 1- and 5 years postdiagnosis were calculated (95% confidence intervals [CIs]). Analyzes were conducted using STATA v.14 using a significance level of $p < 0.05$ (two-tailed).

Results

Sample description

Data were collected for 275 patients comprising 129 (47%) LGG (grade 1 or 2), 77 (28%) HGG (grade 3 or 4), 23 (8%) MB, 10 (4%) PNET, 19 (7%) EP, and 17 (6%) ''other.'' Demographics, symptom, and diagnostic pathway information are shown in Table 1. The majority were male (59%) and between 18 and 24 years of age (67%). Most (83%) patients were treated in adult hospitals.

Presenting symptoms and time to diagnosis

Patients presented with a median of two symptoms (range 1–8): with headache (53%), visual disturbance (31%), nausea (31%), and seizures (25%) the most common. Symptoms varied by tumor type, with nausea more common for MB ($p < 0.01$), and seizures more common for glioma ($p < 0.01$). Symptoms were present for a median of 3 weeks (range 0–520) before presentation to a health professional, although this was longer for MB and EP (both median = 8 weeks) (Table 1). In logistic regression analyzes adjusting for age, gender, and total number of symptoms, AYAs experiencing seizures (odds ratio [OR] = 0.29, 95% CI: 0.09–0.96, $p = 0.027$) and nausea (OR = 0.40, 95% CI: 0.17–0.97, $p = 0.042$) had reduced likelihood of delaying more than 1 month before consulting a health professional. One-third of AYAs first presented to an emergency department (ED), which was more common for HGG and MB ($p = 0.03$), and when symptoms included seizures ($p < 0.001$). Most commonly, patients were referred to a neurosurgeon (either pediatric or adult) and the median time from first consultation to diagnosis was 1 week (range 0–173).

Tumor characteristics and treatment

Tumor characteristics and treatment are shown in Table 1 for each subtype. As expected, tumor location varied by subtype ($p < 0.01$), with a greater proportion of MB located in the posterior fossa and most EP in the spinal cord. Tumor size information was available for 199 cases, with EP tumors the largest at diagnosis. Most patients underwent debulking surgery, with resection noted as less than complete/not reported as complete for 54% with this information missing for 34 cases (13%). Excluding cases with missing data, resection was complete for 47% of those at pediatric hospitals and 36% of those at adult hospitals, which was not statistically significant ($p = 0.18$)

Of 15–17-year-olds, 50% attended a pediatric hospital for treatment. An MDT discussion was recorded in 34% of patients' medical records, with this slightly higher at pediatric (46%) compared with adult (31%) centers ($p = 0.06$). Across tumor types, only 4% of patients were enrolled in a clinical trial.

Low grade glioma. Fifty-three percent of LGG were supratentorial and 30% were in the posterior fossa or spinal cord, with location not recorded for 12%. Tumor size was relatively modest (mean = 38.51 mm), possibly reflecting the availability of imaging modalities in Australia. Nearly all patients had surgery, 15% RT (3% of grade 1; 23% of grade 2), and 12% CT (64% had Temozolomide). While treatment center type was not statistically associated with RT or CT, all patients having Temozolomide had treatment at adult centers.

High-grade glioma. Most HGG were supratentorial with some reported to have an adverse location (posterior fossa 11%, midline 8%, and multifocal 5%). Thirty-two percent of cases had grade 3 disease, 51% grade 4, 12% had grade recorded as high and grade was missing for 5%. All HGG patients had surgery, 81% received RT, and 75% CT (85% Temozolomide), with 71% having both RT and CT. Although patients attending pediatric treatment centers were slightly more likely to have RT (90%) and CT (90%) than those at adult centers (79%, 73%, respectively), these differences were not statistically significant.

Medulloblastoma. Most MB were in the posterior fossa (91%) and 22% were metastatic at diagnosis. All patients had surgery, and 87% had RT and 78% CT (74% had both). Two of the three patients not having RT declined this treatment, with the third patient's reasons not able to be determined. Nine had autologous stem cell support, predominantly on the SJMB 96 study protocol or a variant of this protocol.

Primitive neuroectodermal tumors. Ten PNET (two metastatic at diagnosis) underwent similar treatment to MB, with 80% receiving combined modality therapy, including two who received autologous stem cell support. Of the two patients not having RT, one declined due to rapid disease progression, while reasons could not be determined for the other patient.

Ependymoma. More than half EP were located in the spinal cord. Disease grade was not reported for two cases, whereas 28% had grade 1, 44% grade 2, and 22% grade 3 disease. While a third of the patients had RT, CT was uncommon.

Other types. Seventeen AYAs had CNS tumors of heterogeneous pathologies mainly located in the posterior fossa area (88%), with a mean size of 40.55 mm (SD = 17.56). Most were treated at adult hospitals (88%). Reflecting the heterogeneous pathology, 82% had surgery, 24% had RT, 18% had CT, and 12% had combined therapy.

Relapse and survival

Relapse was noted in 47 cases (17%), and was highest for MB (36%) and lowest for LGG (13%). Relapse occurred a median of 17 months (range: 1–70) postdiagnosis. Median time between diagnosis and follow-up by death registry match for vital status (regardless of whether the individual had died or not) was 80 months (range 46–119 months), with 86 AYAs dying over this interval. RFS and OS estimates are shown in Table 2. Poorest 5-year OS was found for PNET (20% [95% CI: 4–47]) and HGG (42%, [95% CI: 31%–53%]) (Table 2). Survival curves for the different tumor types are shown in Figure 1. As expected, survival was significantly lower for PNET and HGG relative to the other tumor types ($p < 0.01$).

Discussion

This study describes the presentation, treatment, and survival of CNS tumor subtypes in AYAs for a population-based cohort of Australian patients diagnosed between 2007 and 2012. Our national approach means that all patients,

Table 1. Demographic, Diagnostic and Tumor Characteristics, Treatment Location, and Treatment Received by Central Nervous System Tumor Type

	Low grade glioma	*High grade glioma*	*Medulla-blastoma*	*PNET*	*Ependy-moma*	*Other*	*All cases*
	n = *129*	n = *77*	n = *23*	n = *10*	n = *19*	n = *17*	N = *275*
Sex							
Males	58%	62%	70%	40%	47%	53%	59%
Females	32%	36%	30%	60%	53%	47%	41%
Age							
15–17	37%	26%	44%	20%	32%	23%	33%
18–24	63%	74%	56%	80%	68%	77%	67%
Number of symptoms							
Median (range)	2 (1–7)	2 (1–6)	3 (1–8)	2.5 (2–5)	3 (1–5)	2 (1–6)	2 (1–8)
Weeks symptoms present							
Median (range)	3 (0–520)	2 (0–156)	8 (1–52)	6 (1–12)	8 (0–104)	4.5 (0–24)	3 (0–520)
Symptoms experienced (multiple responses allowed)							
Headache	45%	55%	78%	80%	42%	65%	53%**
Visual disturbance	20%	43%	36%	60%	25%	53%	31%*
Nausea	21%	31%	74%	60%	32%	29%	31%**
Seizures	33%	31%	0%	0	5%	6%	25%**
Dizziness	9%	8%	26%	0	5%	12%	10%
Balance	5%	5%	33%	0	0	12%	9%**
Professional first consulted							
Primary care practitioner	48%	43%	44%	30%	50%	56%	46%
ED	30%	46%	44%	30%	17%	19%	34%
Allied health	2%	4%	4%	10%	0	6%	3%
Not recorded	20%	7%	9%	30%	28%[a]	19%	16%
Time to diagnosis from first consult (weeks)[b]							
Median (range)	1 (0–173)	1 (0–173)	2 (0–72)	0.5 (0–66)	2 (0–79)	1 (0–31)	1 (0–173)
Tumor location[c]							
Posterior fossa	26%	11%	91%	20%	21%	88%	30%
Spinal cord	5%	4%	4%[d]	20%	53%	0	8%
Cerebral	52%	45%	0%	30%	16%	6%	53%
Midline	1%	8%	0%	0	11%	0	3%
Other	12%	11%	0%	20%	0	6%	10%
Multifocal	4%	5%	4%[d]	10%	0	0	4%
Tumor size (mm, largest dimension)[c,e]							
Mean (SD)	38.51 (20.5)	46.44 (18.70)	39.13 (13.14)	43.0 (18.44)	52.31 (22.87)	40.55 (17.56)	41.91 (19.80)
Enrolled in clinical trial[c]							
Yes	2%	7%	13%	0%	5%	0	4%
Type of hospital attended[c]							
Adult	81%	87%	74%	100%	84%	88%	83%
Pediatric	19%	13%	26%	0	16%	12%	17%
% of 15–17 year olds attending pediatric hospital[c]							
	n = *48*	*n* = *20*	*n* = *10*	*n* = *2*	*n* = *6*	*n* = 4	*n* = 90
Pediatric	52%	50%	60%	0	33%	50%	50%
Treatment[c]							
Surgery	96%	100%	100%	100%	100%	82%	97%
RT	15%	81%	87%	80%	37%	23%	44%
CT	12%	75%	78%	90%	5%	12%	37%
Combined modality	7%	71%	74%	80%	0	12%	33%
Bone marrow treatment	0	1%	39%	10%	0	0%	4%

*$p < 0.05$, **$p < 0.01$.

[a]Five percent of cases with EP had another type of professional recorded.

[b]Seventy-seven cases had missing data on date of first consultation and are excluded from this analysis.

[c]No significance testing by tumor type undertaken

[d]Case had metastatic disease, with location reflecting disease spread

[e]$N = 199$ for this analysis

CT, chemotherapy; ED, emergency department; EP, ependymoma; PNET, primitive neuroectodermal tumors; RT, radiotherapy; SD, standard deviation.

Table 2. One- and 5-Year Overall Survival and Relapse-Free Survival Estimates for Different Central Nervous System Tumor Subtypes

	Low grade glioma % (95% CI)	*High grade glioma % (95% CI)*	*MB % (95% CI)*	*PNET % (95% CI)*	*EP % (95% CI)*	*All cases % (95% CI)*
OS						
1 year	98% (94–100)	81% (70–88)	100%	80% (41–95)	95% (68–99)	93% (89–95)
5 year	86% (78–91)	42% (31–53)	77% (53–90)	20% (4–47)	89% (64–97)	71% 65–76)
RFS						
1 year	96% (91–98)	78% (67–86)	87% (65–96)	60% (25–83)	89% (64–97)	89% (84–92)
5 years	78% (70–85)	43% (32–53)	70% (47–84)	10% (1–36)	79% (53–92)	66% (60–71)

CI, confidence interval; MB, medulloblastoma; OS, overall survival; RFS, relapse-free survival.

irrespective of where they lived or received treatment, were included. This substantially reduced the risk of selection bias that may occur in case series reporting treatment at single-institution centers.

Presenting symptoms for our cohort were similar to those reported elsewhere.[5] Symptoms were present for a median of 3 weeks before patients attended a health professional, although those experiencing seizures or nausea presented earlier. There is concern that a cancer diagnosis in AYAs may be delayed.[16] While some patients in our study had a very long symptom duration and diagnostic intervals, the median symptom duration for CNS tumors was less than for Australian AYAs with sarcoma (median 12 weeks).[17] Around a third of the patients in our study were diagnosed through the ED. Future studies could explore the impact of this diagnostic route for patients and families on levels of distress experienced.

While surgery is the main treatment modality for CNS tumors, it is unclear whether outcomes for AYAs are improved if a pediatric or adult approach regarding adjuvant CT or RT is adopted.[4] Our results indicate that management of CNS tumors in Australian AYAs depended primarily on tumor type with little influence of treatment location. For example, MB patients were treated on a pediatric-type protocol that included RT and the addition of intensive CT. This pattern of results may reflect the development of specialized AYA treatment centers that began in 2008 across Australia. These centers, generally colocated with the main adult or pediatric cancer service at publically funded tertiary hospitals, are staffed by specialist AYA medical and allied health care professionals.[18] Patients treated in adult centers would be overseen by neuro-oncologists supported by medical and radiation oncologists along with the specialist AYA services.

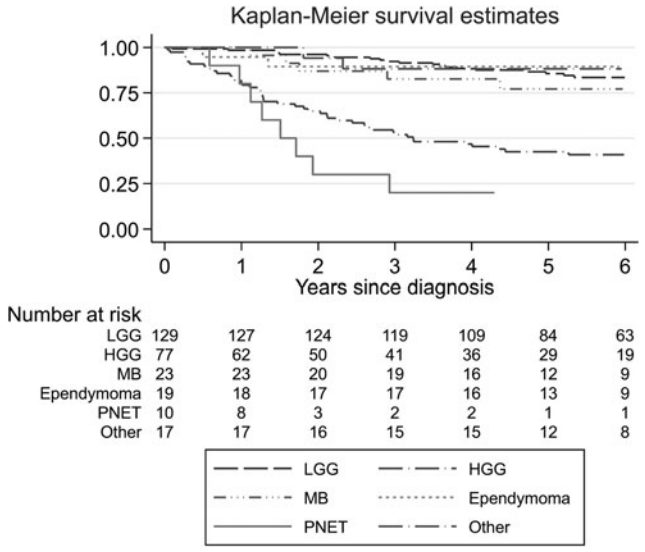

FIG. 1. Overall survival by type of tumor. HGG, high-grade glioma; LGG, low-grade glioma; MB, medulloblastoma; PNET, primitive neuroectodermal tumors.

Treatment aims for pediatric and adult LGG tend to differ, with adult treatment aiming to delay progression to HGGs, while pediatric treatment aims to cure the disease while minimizing possible long-term treatment impacts.[4] Pediatric LGG is more likely to be treated initially with surgery alone, whereas adult protocols include upfront RT for residual disease or other high-risk features. As only 3% of AYAs with grade 1 LGG had adjuvant RT, our study suggests that AYA LGGs are treated in accordance with a pediatric approach. In contrast, most of the AYA patients with HGG received adjuvant RT, which is standard for both adults and children,[4] although the inclusion of Temozolomide-based CT follows adult protocols.

As 80% of PNET patients in our study had RT and CT, treatment for these tumors in Australia mostly follows consensus recommendations.[19] A recent review article[4] suggested that AYAs with MB may benefit from being treated on pediatric protocols that include both RT and CT. A retrospective review of 751 adult patients with MB (median age 29 years) found better 5-year OS for those treated with combination CT/RT (OS = 86%) compared with RT alone (72%).[20] In our study, nearly three-quarters of AYAs with MB received adjuvant CT and RT, suggesting that clinicians in Australia have largely adopted this practice.

The paucity of research examining patterns of care for AYA populations with different CNS subtypes[9] makes it difficult to compare our findings to other jurisdictions. A United Kingdom study of AYA CNS tumors diagnosed between 1990 and 2009 found that CT use increased over time.[9] Although the United Kingdom study did not stratify treatment by tumor subtype, our finding that CT was commonly included in treatment protocols for HGG, MB, and PNET is in line with its findings. Our findings are also analogous with findings from a United States study that showed patients 0–39 years of age with HGG diagnosed between 2004 and 2012 were more likely to receive CT than those with low-grade tumors[10] consistent with recent findings suggesting that the addition of CT for HGG can improve outcomes.[21] The United States study reported RT use in 65% of HGG patients.[10] In our study, 81% of HGG and 85% of

MB patients received RT. The inclusion of patients under 15 years of age in the United States study may explain some of this difference.

Comparisons of the 5-year survival rates in this study with previous Australian and international cohorts are difficult due to changes in CNS tumor nomenclature and different age groups included in the AYA definition. A previous Australian study estimated a 5-year OS at 66% for all CNS tumors,[22] which is slightly lower than the 71% in the current study. A French study estimated a 5-year survival at 67% for all CNS tumors diagnosed between 2000 and 2004.[23] A United States study estimated a 5-year survival for 15–19-year-olds and those over 20 diagnosed with MB between 2001 and 2013 at 72% and 74%, respectively.[24] A German study estimated a 5-year survival at 39% for 15–29-year-olds with glioblastoma diagnosed in the period 2002–2006 and 76% for low-grade astrocytomas.[25] While our 5-year survival rates for LGG and EP were promising, the 20% survival rates for PNET and 42% for HGG tumors demonstrate the continuing poor outcomes for some CNS tumor subtypes, but seem broadly similar to other published studies.

The lack of improvements in survival in AYAs and the extremely poor survival rates for some CNS tumor subtypes emphasize the need for more research in this area, including more clinical trials. The low rate of clinical trial enrolment for this cohort likely reflects both the lack of suitable trials for AYAs and the overall paucity of trials available for rare cancers. Higher rates of trial participation have been found for AYAs treated at pediatric compared with adult hospitals,[26] hence strategies to increase AYAs' trial participation in adult hospitals, where most AYAs in Australia are treated, are needed. The Australian government has provided an additional $3 million ($AU) to fund new clinical trials in AYA cancer, with one of the funded trials focusing on MB. Trials for other low survival CNS tumors are needed.

This study's greatest strength is its population-based approach to case identification, obtaining data for a national sample of patients and high case ascertainment rate for data collection. However, despite our national approach, our relatively small sample size (especially for some tumor subtypes) is a key limitation. While the small numbers reflect the rarity of these tumors, it limited our ability to detect all but large differences in outcomes and prohibited the use of multivariable analyzes to determine factors influencing survival outcomes within tumor types. As data were extracted from individual medical records, it is only as accurate as the information recorded. Gaps in the information recorded may have led to underreporting of treatment. This might be influencing our findings for MDT discussions. As many patients were treated by two or three modalities it is possible that some MDT discussions were held but not documented in patient records. We attempted to collect treatment information from all hospitals that patients attended for their initial care, but permission was not granted at some private hospitals. Although this meant we may not have the details of specific care delivered at these hospitals, medical records generally recorded the type of treatment these centers had delivered. While we assessed a 5-year survival, follow-up for 22% of the sample was between 46 and 59 months. This may have influenced our survival estimates.

Despite these limitations, this is the first population-based study to describe treatment for Australian AYA CNS tumor patients. Our study suggests that in the modern era, type of treatment center attended did not greatly influence the care of Australian AYAs with CNS tumors. Future studies need to explore whether modifiable factors, including trial participation and presentation at an MDT can be improved across the board for AYAs with CNS tumors.

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Address correspondence to:
Victoria M. White, PhD
School of Psychology
Deakin University
221 Burwood Highway, Burwood
Victoria 3125
Australia

Email: vicki.white@deakin.edu.au