

Guidelines for Treatment and Monitoring of Adult Survivors of Pediatric Brain Tumors

Anna J. Janss, MD PhD^{1,}*

Claire Mazewski, MD¹

Briana Patterson, MD²

Address

^{*1}Neuro-Oncology, Aflac Children's Cancer and Blood Disorders Clinic/Emory Pediatric Institute, 5461 Meridian Mark Road, Suite 400, Atlanta, GA, 30342, USA
Email: anna.janss@choa.org

²Pediatric Endocrinology, Emory Children's Center/Emory Pediatric Institute, 2015 Uppergate Drive, Room 232, Atlanta, GA, 30322, USA

© Springer Science+Business Media, LLC, part of Springer Nature 2019

This Article is part of Topical Collection on *Neuro-oncology*

Keywords Pediatric brain tumor survivors · Long-term cancer survivor guidelines · Hypothalamic syndromes · Treatment-induced secondary malignancies · Radiation-induced cognitive impairment · Frailty

Opinion statement

Pathologies of pediatric brain tumors are more varied than those diagnosed in adults and survival outcomes more optimistic. Therapies for pediatric brain tumors are also diverse and treatment options are expanding. The growing number of adult survivors of childhood brain tumors is quite diverse. Medical management of these adults requires understanding the tumor diagnosis and location, the modalities used to treat the tumor, the age of the survivor at the time of diagnosis and treatment, any complications of treatment, and, most importantly, the baseline medical condition and neurological function of each adult survivor. A network of medical, neurological, and mental health providers is critical in the care of a child with a brain tumor. A comparable network should be available to survivors of these tumors since they may transition to adulthood with medical and neurological deficits and can acquire additional late effects of treatments as they age. Optimally, each survivor will have an individualized survivor health plan (SHP) that concisely summarizes the tumor, treatments, potential late effects, and screening that may identify evolving late effects before they impact mental, social or physical functioning. This plan helps patients, families, and the medical team advocate for surveillance aiming to optimize the survivor's quality of life. Failure to support the health and function of these heroic cancer survivors renders the medical advances, the courage, and the struggle that permitted survival meaningless.

Introduction

The incidence and survival of children diagnosed with brain tumor has gradually increased over the last 20 years [1]. Improved survival for low-grade and malignant pediatric brain tumors is likely due to improvements in detection, diagnosis (clarification and uniform pathologic criteria and molecular diagnostic tools), neurosurgical techniques, and therapy including conformal radiation techniques, intensification of standard chemotherapy, targeted or precision tumor treatments, and increased participation in clinical trials [1–3]. Etiologies for increased incidence, particularly in younger patients [1, 3] are not clear, but cannot be ascribed to improved sensitivity and wider availability of neuro-imaging. Regardless of cause(s), the consequence of increased incidence and improved survival is a wave of adult survivors of childhood brain tumors transitioning from pediatric oncology care to adult care, with a worldwide incidence rate of as much as 5 per 100,000 annually [1, 3, 4].

Survivors of childhood brain tumors, like all cancer survivors, require screening for late effects of cancer therapies, regular surveillance for tumor recurrence, and surveillance for development of secondary malignancies. Evidence-based long-term follow-up guidelines for screening late effects of therapies for childhood, adolescent, and young adult cancer are regularly updated by the Children's Oncology Group (COG) and are available online (<http://www-survivorshipguidelines.org>).

Survivors of childhood brain tumors have additional and unique risks for medical, neurologic, cognitive, and psychosocial morbidities as their disease and treatment impact the developing central nervous system. Research in this population is growing, but not abundant. This chapter will outline recommended surveillance for adult survivors of pediatric brain tumors organized by the treatment, surveillance for unique medical morbidities, and surveillance for secondary malignancy that augment, not repeat the guidelines provided by COG. For the purposes of this chapter, adults will be defined at individuals at least 19 years of age.

Risk for tumor recurrence varies with tumor pathology and time post-diagnosis. Over time, the risk for primary tumor recurrence decreases, and the risk for secondary malignancy and medical morbidity increases [5]. Effective monitoring of adult survivors of childhood brain tumors includes familiarity with that patient's medical history, specifically the timing, pathology, and treatment of the brain tumor. For example, a 20-year-old patient diagnosed and treated for a malignant brain tumor (e.g., medulloblastoma, ependymoma, or malignant glioma) at the age of 17 should be followed closely for tumor recurrence by multi-specialty services (neuro-oncology, radiation oncology, neurosurgery) to permit early detection of recurrence that will increase treatment efficacy of the recurrence, or palliation of its symptoms. An adult of similar age diagnosed and treated for CNS malignancy at age 5 will have less risk of primary tumor recurrence, and the focus of care will be medical monitoring for late effects of therapy. An adult treated for a low-grade CNS tumor such as a pilocytic astrocytoma will also need monitoring for tumor recurrence/progression, but the risk will depend on the extent of tumor resection and the time from diagnosis and treatment. Unfortunately, these low-grade tumors can recur following gross total resection and can progress after years of quiescence [6••]. Adult survivors of pediatric brain tumors are also at increased risk (compared to sibling cohort) for late-onset neurologic deficits (headaches, seizures, coordination problems, motor problems, vision problems, and vertigo), psychiatric disease, endocrine, circulatory, musculoskeletal, and renal dysfunction [7, 8]. Clearly, regular medical care and thorough neurologic examination is a critical part of monitoring all adult survivors of childhood brain tumors.

Recommendations regarding intervals of surveillance for tumor recurrence are a function of tumor pathology and biology. They will not be discussed here due to space limitation.

Tumor treatment with surgery alone

Hydrocephalus

Over half of children with brain tumors present with hydrocephalus [9]. This has implications for cognitive and neurological deficits independent of subsequent therapy [10, 11]. While ventriculoperitoneal shunt (VPS)

insertion has been the standard for treatment of the hydrocephalus, the trend is to delay and avoid placement by more aggressive tumor resection, use of third ventriculostomy, subdural peritoneal shunts and gradual weaning of cerebrospinal fluid (CSF) diversion with external ventricular drains [9, 10]. Those adult survivors of pediatric brain tumors who have an indwelling VPS suffer higher mortality and morbidity compared to siblings or cancer survivors without VPS and are at risk for shunt malfunction decades post-insertion [9–11].

Monitoring these patients should include neurologic screening due to increased risk of late-onset epilepsy and other CNS deficits (motor, sensory, behavioral) [10, 11]. Facilitating access to mental health specialists and social work is another important part of care as over 20% of adults who had VP shunts placed in childhood (independent of cancer diagnosis) were unable to integrate into a competitive work place [10, 11]. These survivors also struggle with social integration as measured by reports of living independently or living with a spouse or partner [10, 11]. It is also recommended that they have access to, or regular surveillance by neurosurgery, to expedite evaluation of potential VPS infection or malfunction.

Posterior fossa

Speech

Integration of speech, oculomotor, and motor learning reside within brainstem, cortical and cerebellar networks [12], so it is not surprising that these functions are often impaired in survivors of posterior fossa tumors following extensive resection [13–16]. The phenomenon of transient *cerebellar mutism* or *posterior fossa decompression syndrome* has been reported in a significant number of children following resection of large tumors of the cerebellum [13, 14], but Huber and colleagues have demonstrated that the impact on performance IQ, speech, and reading are not transient [15]. In separate work, the same group demonstrated that adult survivors of cerebellar tumors without transient cerebellar mutism exhibited slower speech patterns (ataxic dysarthria, dysfluency, and slower speech rate) than controls and that this phenomenon was exacerbated by irradiation [16].

Visual-motor function

Oculomotor function is as important as acuity and visual field integrity to reading, ambulating, and posture [17]. Posterior fossa structures including cranial nerves and nuclei, the medial longitudinal fasciculi of the pons, and rostral medial longitudinal fasciculi of the midbrain as well as cortico-cerebellar and deep cerebellar nuclei are involved in coordination of eye movements [18]. These are impaired in children with posterior fossa tumors [19]. While surgical interventions and prism lenses can repair dysconjugate gaze, they do not correct problems within smooth and saccade visual pursuits. These deficits remain through childhood, school age, and into adulthood, which will impact education and reading skills; although, studies to evaluate this are outstanding.

Attention/cognition

Interconnection of cortical, primarily frontal, brainstem, and cerebellar structures is involved in maintaining attention [20, 21]. Not surprisingly, almost a quarter of survivors of childhood brain tumors demonstrate symptoms of attention deficit disorder, many independent of radiation or chemotherapy [22]. Presence of symptoms of attention deficit appears to exacerbate other neuro-cognitive impairments such as IQ, processing speed, executive functioning, and psychosocial function [21, 22]. Behavioral and pharmacotherapies improve performance in these patients [7, 21], but impact on educational and behavioral outcomes in adult survivors of childhood brain tumors has not been studied.

Implications of the above are that communication with, and care of adult survivors of cerebellar tumors will take extra time and patience. Reading assistance and social services will benefit the patients, caregivers, and providers. Regular ophthalmology examinations may detect and ameliorate oculomotor dysfunction that can deteriorate with age. Providers should be ready to screen for signs and symptoms of adult attention deficit disorder and provide access to programs for cognitive remediation and/or stimulant medication to help with attention and performance.

Cerebral cortex

Neurological deficits that follow surgical resection of tumors in the cerebral cortex may be avoided by pre-operative studies such as functional MRI and diffusion MRI tractography [23, 24], though they often improve with time and rehabilitation [25]. Unmasking of these neurologic deficits by metabolic insults such as systemic illness, intoxication, or sleep deprivation can be frightening, raising concerns of tumor recurrence, but should resolve when the insult has abated. However, if the symptoms and signs do not resolve, thorough evaluation, including imaging, is indicated. Brain tumor survivors are at higher risk for late-onset neurological morbidities such as epilepsy, migraine, and demyelination even without history of radiation or chemotherapy [7, 8].

Adult survivors of childhood brain tumors require periodic physical examination and neurological screening. Medical care providers must be familiar with baseline function and make appropriate referral to neurology for neuro-radiology studies if there is persistent decline from the baseline.

Hypothalamus/supratentorial midline

Over 10% of pediatric brain tumors occur in or near the third ventricle [26•]. The pathologies for these tumors vary from the highly malignant (e.g., mixed germ cell tumors) to less aggressive tumors (e.g., pilocytic astrocytomas, craniopharyngiomas), to tumors that do not grow at all (e.g., hamartomas). While they represent a small fraction of childhood brain tumors, the overall survival rate is high [6••, 26•, 27], so attention to monitoring of survivors of pediatric hypothalamic and supratentorial midline tumors is essential.

Children with supratentorial midline tumors often present with endocrinopathies, abnormal vision, cognition, and behavior [26•, 27, 28]. Surgical resection or biopsy of tumors in eloquent structures near the chiasm or medial hypothalamus can cause new or worsen existing endocrine dysfunction and cognitive impairment. The domains of memory, impulsivity, sleep, and

satiety are most vulnerable [26•, 27–29, 30•]. These are tumors that rarely kill, but always maim.

Endocrinopathies

Patterns of endocrine dysfunction are associated with, but not exclusive to, the presentation of different hypothalamic tumor pathologies. Impairment of anterior pituitary functions such as secondary adrenal insufficiency, TSH/TRH deficiency, pubertal arrest, and/or mild hyperprolactinemia can manifest over time in children with large hypothalamic tumors [26•]. Patterns of endocrine dysfunction post-resection or biopsy of supratentorial midline tumors are a function of the location, extent, and complications of the surgery [26•, 27, 28].

Obesity

Hypothalamic obesity, a poorly understood condition that results from hyperphagia and dysregulation of anorexigenic and orexigenic hormones can be seen in children who do not have surgery, but is more common after surgery [27, 28, 31]. It is manifested as morbid exponential increase in weight (BMI > +3 SDS) [26•] that is refractory to approaches used to manage other forms of obesity such as calorie restriction and medical or surgical interventions [32]. Hypothalamic obesity confers increased mortality and morbidity independent of its detrimental impact on quality of life [26•, 28, 31].

Hypersomnia/autonomic dysfunction

Hypersomnia, or excessive daytime sleepiness, is manifest in survivors of a variety of childhood brain tumors with rates as high as 1670/100,000 [33]. Tumor location in the supratentorial midline location is a more robust predictor of sleep pathology than irradiation or treatment with anti-epileptic medications [33]. Sleep pathologies include narcolepsy, obstructive sleep apnea, and central sleep apnea. Thermal and cardiovascular instability is seen in children with tumors in the medial hypothalamus and can accompany and complicate hypothalamic obesity [26•, 28, 30•]. Its most aggressive manifestation is in the relatively newly identified condition of rapid-onset obesity with hypoventilation, hypothalamic, and autonomic dysregulation (ROHHAD), a condition associated with neuronal and hypothalamic tumors in young children that can lead to cardiovascular arrest and death [34]. Sympathetic and cardiovascular autonomic dysfunction localize to the hypothalamic-midbrain interface [35, 36] and may exist in survivors of childhood brain tumors in patterns less aggressive than ROHHAD [30•].

Cognition/psychiatric disorders

Children with supratentorial midline tumors demonstrate significant deficits in visual memory and visual spatial analysis even prior to surgery [29]. Problems with learning and memory, executive function, and fine motor coordination have also been documented prior to radiation therapy [37]. Following surgical intervention, a variety of cognitive and psychiatric disorders may manifest (e.g., Korsakoff-like memory deficits, behavior/

personality changes, impaired emotional control, cognitive impairment, mood alteration, and psychotic symptoms). Careful clinical documentation of cognitive and psychiatric changes and associated hypothalamic damage has recently generated a model for the neurobiological basis for cognitive and psychiatric disorders [30•].

Vision

Almost 40% of children with hypothalamic/pituitary tumor present due to alterations in vision [38]. Therapeutic interventions may reverse the vision loss [39, 40]. More often, the visual impairment persists and can deteriorate months to years following presentation [39]. Neuro-ophthalmologic deficits may persist in this patient population along with endocrine dysfunction, sleep disorders, and obesity [38], but they have independent negative impact on quality of life [41].

Thus, the scope of medical attention and social support needed to follow adult survivors of childhood hypothalamic tumors is extensive. Most survivors of hypothalamic tumors will have established hormone replacement needs at the time of transition to adult care, but those diagnosed and treated as young adults may develop additional endocrinopathies, benefit from dose adjustments, adult dosing of growth hormone replacement [42], or reproductive counseling [43]. Monitoring of endocrine function is recommended every 1 to 2 years for survivors of childhood hypothalamic tumors who have transitioned to adult care. More frequent evaluation of endocrine function *and* electrolytes are critical for survivors diagnosed with diabetes insipidus with adipsia (loss of thirst mechanism). Aggressive (annual) monitoring and management of weight and the morbidities of obesity and hyperlipidemia are imperative. Mortality in adult survivors of craniopharyngioma therapy is less likely to be due to tumor recurrence and progression, and more likely to be due to cardiovascular, endocrine, hepatic, or infectious complications [26•, 27, 28]. Referral to sleep medicine is recommended for any survivors demonstrating excessive daytime sleepiness or fatigue as the etiology may be a complex mix of abnormal circadian rhythms, central apnea, or obstructive apnea. Correction of the sleep disorder can improve endocrine function, weight control, and problems with behavior and cognition, with attendant increased quality of life and health [44]. Problems with memory impairment and/or psychiatric disorders handicap management of metabolic and endocrine disorders. Medical, ophthalmological, and neurological surveillances are important for monitoring adult survivors of pediatric supratentorial midline tumors. A network of social, legal, financial, and mental health supports may optimize care of and improve outcomes for this group of young high-risk patients.

Tumor treatment with cranial or craniospinal radiation

Deleterious impact of radiation therapy on the developing nervous system has been well documented. Impact increases with dose and volume of radiation

and as age at time of radiation decreases [45, 46•]. Equally well documented is the efficacy of radiation for treatment of malignancies of the CNS. The tension between these two truths has inspired strategies to reduce the volume and dose of radiation or delay radiation treatments. Regardless of these strategies, the efficacy of radiation for tumors at presentation and relapse means many adult survivors of irradiated pediatric brain tumors will transition to adult care. Recommendations for screening of endocrine, cardiovascular, pulmonary, vision, and hearing in survivors of cranial irradiation can be found in COG long-term follow-up guidelines (<http://www.survivorshipguidelines.org>) and will not be discussed here. This section will focus on technologies to predict, monitor, and ameliorate the impact of cranial and craniospinal irradiation in adult survivors of pediatric brain tumors.

Cognition

The scope of cognitive impairments associated with cranial irradiation includes marred executive function, memory, attention, processing speed, and global cognitive abilities. A seminal Childhood Cancer Survivor Study reported that the target of cerebral radiation also impacts cognitive and performance outcomes with the temporal lobe demonstrating the greatest sensitivity to radiation effects on memory and intellect [45, 46•]. These impairments impact health-related quality of life of adult survivors of childhood cancer [45–47]. Cerebrovascular injury is the putative etiology of late cognitive impairment. Radiation-induced vasculopathies such as microbleeds, cavernous malformations, and cavernomas can be seen in the cerebral imaging of brain tumor survivors. The amount of cerebral microbleeds correlates with the dose of radiation and the degree of cognitive impairment [48].

Cerebrovascular disease

COG long-term follow-up guidelines include recommendations for assessing for accelerated cerebrovascular disease including atherosclerotic occlusion of carotid arteries, moyamoya, and cavernomas. Survivors of irradiated childhood brain cancer with inherited predisposition to vascular disease such as neurofibromatosis type I or sickle cell disease are likely to present earlier and with greater morbidity [49, 50]. Cranial irradiation of > 50 Gy increases the risk of stroke by 1% at 12 years and 12% at 30 years post-treatment [46•].

Secondary malignancy

The risk of secondary malignancy following radiation is a function of radiation dose, age at time of radiation, and existence of inherited predisposition to cancer. Monitoring for radiation-induced tumors of the skin and bones is outlined in COG long-term follow-up guidelines. The International Late Effects of Childhood Cancer Guidelines Harmonization Group is a body of multiple experts in childhood cancer and survivorship from multiple countries working to reconcile evidence based guidelines around the world [5]. Their conclusions are that there is a dose-dependent increase in the risk of CNS tumors in children treated with cranial irradiation and that this risk does not plateau over time. They are poised to release recommendations for

monitoring for radiation-induced brain tumors in adult survivors of childhood cancer. They recommend that providers should be aware of the risk of development of secondary CNS malignancy and counsel survivors to report symptoms consistent with development of a new CNS tumor (escalating headaches, new onset motor, cognitive, sensory or behavioral changes, new onset or worsening seizures, or other focal neurological defects). Surveillance of adult survivors of irradiated childhood brain tumors should include annual neurological examination to screen for new deficits that could herald developing a secondary malignancy or vasculopathy. Wells et al. recently noted that the risk of new-onset neurologic problems (headaches, blindness, hearing loss, seizures, coordination problems) increases without plateau even 30 years after radiation [46•]. Magnetic resonance imaging with and without contrast is the most sensitive modality to identify tumors of the central nervous system. Regular surveillance imaging is not recommended due to financial and emotional stress the survivor may experience, the potential of identifying incidental conditions that could result in unnecessary studies and procedures, and finally the lack of evidence that early identification of secondary malignancy will change outcome [5]. Conversely, vision and hearing screens every 1 to 2 years and protection of sensory function are important because these patients are at risk for further impairment of vision and hearing. Survivors with neurological, cognitive, or behavioral deficits become more isolated when sensory function decreases resulting in worsened social function as measured by living independently, graduating high school, and finding employment. This detriment is independent of, and adds to, that caused by cognitive impairment alone [51–53].

Chemotherapy

Cognition

Treatment with intensive chemotherapy with or without stem cell rescue contributes to cognitive impairment in survivors of non-CNS malignancies [53]. Comparative studies to evaluate how intensive chemotherapy regimens impact cognition and behavior in survivors of CNS tumors are rare. While deleterious impact of chemotherapy on cognitive function appears to be less than that caused by craniospinal radiation in survivors of pediatric brain tumors, monitoring for changes in memory and behavior remains important and referral to appropriate specialties (neurology, psychology, social services, rehabilitation) may improve function and quality of life.

Secondary malignancy

Treatment with intrathecal methotrexate, a therapy commonly used for myeloid malignancies, and occasionally used for embryonal brain tumors such as atypical teratoid rhabdoid tumors, may increase the risk of secondary meningioma [5].

Treatment-specific impact of different anti-tumor therapies on health and hearing with attendant recommended surveillance can be found in COG

long-term follow-up guidelines. Biologically targeted agents are now more common in the treatment of pediatric brain tumors and have distinct endocrine, dermatologic, cardiovascular and ophthalmologic toxicities, and potential late effects [6••,26•,28]. Long-term guidelines are periodically updated and will include recommendations for appropriate surveillance as we enter the age of precision medicine.

Chemotherapy + radiation

Chemotherapy given prior to, during and after radiation therapy can potentiate anti-cancer therapy, but also compound toxicity [45, 46•].

Hearing

Cisplatin and high-dose carboplatin injure the hair cells of the cochlea resulting in permanent high-frequency hearing loss. This loss is additive to the impact of cranial radiation on hearing [51–53].

Secondary malignancy

There is not good data to support evidence that treatment with alkylating or platinating anti-cancer therapies increases the risk of radiation-induced CNS tumors in adult survivors [5].

Frailty

Frailty, defined as new-onset chronic health conditions and mortality, is a condition shared by older adults and childhood cancer survivors. Geriatric medical practices have proven an informative model to identify poor fitness, muscular weakness, and cognitive decline in young adult cancer survivors [54]. This premature aging of adults exposed to radiation and/or chemotherapy during treatment of pediatric brain tumors is likely grounded in the mechanism of action of chemotherapy agents on the biological processes of senescence [55•].

Primary care providers can model the clinical monitoring of young adult survivors of CNS cancer on the geriatric model used for health surveillance of adults 10–20 years older, but without a history of radiation or chemotherapy.

Summary

Survivors of childhood brain tumors are not uniform in pathology, location, treatment, or complications. Medical providers monitoring them as they transition to adult care must be familiar with individual history, medical condition, and neurological deficits of each survivor to appropriately evaluate for risk of tumor recurrence and treatment late effects that impact health-related quality of life.

Specialty clinics to follow these survivors may improve quality of life outcome [54], but are not available or necessary for all these survivors [56]. Surveillance recommendations in the long-term follow-up guidelines and individualized survivor health plans are helpful in early detection of late effects of cancer therapy [57]. Annual neurologic screens and low threshold to refer to specialists for problems with hearing, vision, endocrine, sleep, and mental health are indicated for these patients with high risk for medical, neurologic, cognitive, and psychological morbidity. Regular imaging of the brain is *not* indicated in the absence of clinical change unless the survivor has an inherited predisposition to cancer or vasculopathy. Coordination of medical care with social services, vocational supports, and cognitive rehabilitation may promote wellness and positive outcomes [28].

Compliance With Ethical Standards

Conflict of Interest

Anna J. Janss, Claire Mazewski, and Briana Patterson declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. Patel S, Bhatnagar A, Wear C, Osiro S, Gabriel A, Kimball D, et al. Are pediatric brain tumors on the rise in the USA? Significant incidence and survival findings from the SEER database analysis. *Childs Nerv Syst.* 2014;30:147–54.
 2. Mueller S, Chang S. Pediatric brain tumors: current treatment strategies and future therapeutic approaches. *Neurotherapeutics.* 2009;6:570–86.
 3. Steliarova-Foucher E, Stiller C, Kaatsch P, Berrino F, Coebergh JW, Lacour B, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. *Lancet.* 2004;364:2097–105.
 4. Madanat-Harjuoja LM, Pokhrel A, Kivivuori SM, Saarinen-Pihkala UM. Childhood cancer survival in Finland (1953-2010): a nation-wide population-based study. *Int J Cancer.* 2014;135:2129–34.
 5. Bowers DC, van der Pal H, Mulder R, Armstrong G, Khan R, Sadighi Z, Klimo P, Bhangoo R, Sabin N, Jenkinson H, Garwicz S, Ng A, Haupt R, Sugden E, Ronckers C, Teepen J, Hawkins M, Reulen R, Schouten-van Meeteren N, Ullrich N, Scheinemann K, Pretorius P, Walker A, Hudson MM, Kremer L, Skinner R, Constine S. Recommendations for surveillance for subsequent tumors of the central nervous system among childhood cancer survivors: a report from the international late effects of childhood cancer guideline harmonization group in collaboration with the pancaresurfup consortium. Manuscript in preparation.
 6. •• Krishnatry MD, Zhukova N, Guerreiro Stucklin AS, Pole JD, Mistry M, Fried I, et al. Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: a population-based study. *Cancer.* 2016;122:1261–9

- This landmark retrospective study of 1202 patients diagnosed with low grade gliomas demonstrated significantly lower long term survival for adult survivors treated with radiation therapy in childhood.
7. Wells EM, Ullrich NJ, Seidel K, Leisenring W, Sklar CA, ARmstron GT, et al. Longitudinal assessment of late-onset neurologic conditions in survivors of childhood central nervous system tumors: a childhood Cancer survivor study report. *Neuro-Oncology*. 2017;20:132–42.
 8. Gunn ME, Malila N, Lahdesmaki T, Arola M, Gronroos M, Matomaki J, et al. Late new morbidity in survivors of adolescent and young-adulthood brain tumors in Finland: a registry-based study. *Neuro-Oncology*. 2015;17:1412–8.
 9. Wong TT, Liang ML, Chen HH, Chang FC. Hydrocephalus with brain tumors in children. *Childs Nerv Syst*. 2011;27:1723–34.
 10. Paulsen AH, Lundar T, Lindegaard KF. Pediatric hydrocephalus: 40-year outcomes in 128 hydrocephalic patients treated with shunts during childhood. Assessment of surgical outcome, work participation, and health-related quality of life. *J Neurosurg Pediatr*. 2015;16:633–41.
 11. Vinchon M, Baroncini M, Delestret I. Adult outcome of pediatric hydrocephalus. *Childs Nerv Syst*. 2012;28:847–54.
 12. Tirapu-Ustarroz J, Luna-Lario P, Iglesias-Fernandez MD, Hernaez-Goni P. Cerebellar contribution to cognitive process: current advances. *Rev Neurol*. 2011;53:301.
 13. Catsman-Berrevoets CE, Aarsen FK. The spectrum of neurobehavioural deficits in the posterior fossa syndrome in children after cerebellar tumour surgery. *Cortex*. 2010;46:933–46.
 14. Korah MP, Esiashvili N, Mazewski CM, Hudgins RJ, Tighiouart M, Janss AJ, et al. Incidence, risks, and sequelae of posterior fossa syndrome in pediatric medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2010;77:106–12.
 15. Huber JF, Bradley K, Spiegler BJ, Dennis M. Long-term effects of transient cerebellar mutism after cerebellar astrocytoma or medulloblastoma tumor resection in childhood. *Childs Nerv Syst*. 2006;22:132–8.
 16. Huber JF, Bradley K, Spiegler BJ, Dennis M. Long-term neuromotor speech deficits in survivors of childhood posterior fossa tumors; effects of tumor type, radiation, age at diagnosis and survival years. *J Child Neuro*. 2007;22:848–54.
 17. Bucci MP, Ajrezo L, Wiener-Vacher S. Oculomotor tasks affect differently postural control in healthy children. *Int J Dev Neurosci*. 2015;46:1–6.
 18. Guillaume A, Fuller JR, Srimal R, Curtis CE. Cortico-cerebellar network involved in saccade adaptation. *J Neurophysiol*. 2018;120:2583–94.
 19. Peeler CE. A review of visual and oculomotor outcomes in children with posterior fossa tumors. *Semin Pediatr Neurol*. 2017;24:100–3.
 20. Szekely E, Sudre GP, Sharp W, Leibenluft E, Shaw P. Defining the neural substrate of the adult outcome of childhood ADHD: a multimodal neuroimaging study of response inhibition. *Am J Psychiatry*. 2017;174:867–76.
 21. Mulhern RK, Merchant TE, Gajjar M, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncol*. 2004;5:399–406.
 22. Hardy KK, Willard VW, Gioia A, Sharkey C, Walsh KS. Attention-mediated neurocognitive profiles in survivors of pediatric brain tumors: comparison to children with neurodevelopmental ADHD. *Neuro-Oncology*. 2018;20:705–15.
 23. Castellano A, Cirillo S, Bello L, Riva M, Falini A. Functional MRI for surgery of gliomas. *Curr Treat Options Neurol*. 2017;19:34.
 24. Lorenzen A, Groeschel S, Ernemann U, Wilke M, Schuhamann MU. Role of presurgical functional MRI and diffusion MR tractography in pediatric low-grade brain tumor surgery: a single-center study. *Child Nerv Syst*. 2018; in press;34:2241–8.
 25. Vargo M. Brain tumor rehabilitation. *Am J Phys Med Rehabil*. 2011;90:S50–62.
 26. Gan HW, Bulwer C, Spoudes H. Pituitary and hypothalamic tumor syndromes in childhood. In: De Groot LJ, Chousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2017.
- Thorough and excellent review of clinical presentation and syndromes seen in children with hypothalamic and pituitary brain tumors.
27. Stripp DCH, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwien JW, et al. Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. *Int J Radiation Oncology Biol Phys*. 2004;58:714–20.
 28. Muller HL. Craniopharyngioma and hypothalamic injury: latest insights into consequent eating disorders and obesity. *Curr Opin Endocrinol*. 2016;23:81–9.
 29. Iuvone L, Peruzzi L, Colosimo C, Tamburrini G, Caldarelli M, DiRocco C, et al. Pretreatment neuropsychological deficits in children with brain tumors. *Neuro-Oncology*. 2011;13:517–24.
 30. Pascual JM, Prieto R, Castro-Dufourny I, Mongardi L, Rosdolsky M, Strauss S, Carrasco R, Barrios L. Craniopharyngiomas primarily involving the hypothalamus: a model of neurosurgical lesions to elucidate the neurobiological basis of psychiatric disorders. *World Neurosurg*. 2018;120:e1245–78.
- Retrospective evaluation of 210 patients with psychiatric disorders caused by craniopharyngiomas. The authors associate the type of psychiatric disturbance with the location of hypothalamic damage to generate a model for neurologic localization of distinct psychiatric disorders.
31. Adachi M, Tsuchiya T, Muroya K, Asakura Y. Prevalence of obesity, hyperlipemia and insulin resistance in children with suprasellar brain tumors. *Clin Pediatr Endocrinol*. 2007;16:1–9.

32. Wang KW, Chau R, Fleming A, Banfield L, Singh SK, Johnston DL, et al. The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. *Obes Rev*. 2017;18:899–914.
33. Khan RB, Merchant TE, Sadighi ZS, Bello MS, Lu Z, Sykes A, et al. Prevalence, risk factors and response to treatment for hypersomnia of central origin in survivors of childhood brain tumors. *J Neuro-Oncol*. 2018;136:379–84.
34. Bougneres P, Pantalone L, Linglart A, Rothenbuhler A, Le Stunff C. Endocrine manifestations of rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation and neural tumor syndrome in childhood. *J Clin Endocrinol Metab*. 2008;93:3971–80.
35. Chow C, Fortier MV, Das L, Menon AP, Vasanwala R, Lam JC, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome may have a hypothalamus-periaqueductal gray localization. *Pediatr Neurol*. 2015;52:521–5.
36. Goh KY, Conway EJ, DaRosso RC, Muszynski CA, Epstein FJ. Sympathetic storms in a child with midbrain glioma: a variant of diencephalic seizures. *Pediatr Neurol*. 1999;21:742–4.
37. Fourniere-Goodnight AS, Ashford JM, Merchant TE, Boop FA, Indelicato DJ, Wang L, et al. Neurocognitive functioning in pediatric craniopharyngioma: performance before treatment with proton therapy. *J Neuro-Oncol*. 2017;134:97–105.
38. Taylor M, Couto-Silva AC, Adan L, Trivin C, Sainte-Rose C, Zerah M, et al. Hypothalamic-pituitary lesions in pediatric patients: endocrine symptoms often precede neuro-ophthalmic presenting symptoms. *J Pediatr*. 2012;161:855–63.
39. Wan MJ, Zapotocky M, Bouffet E, Bartels U, Kulkarni AV, Drake JM. Long-term visual outcomes of craniopharyngioma in children. *J Neuro-Oncol*. 2018;137:645–51.
40. Nair AG, Pathak RS, Iyer VR, Gandhi RA. Optic nerve glioma: an update. *Int Ophthalmol*. 2014;34:999–1005.
41. Jariyakosol S, Peragallo JH. The effects of primary brain tumors on vision and quality of life in pediatric patients. *Semin Neurol*. 2015;35:587–98.
42. Höybye C, Christiansen JS. Growth hormone replacement in adults- current standards and new perspectives. *Best Pract Res Clin Endocrinol Metab*. 2015;29:115–23.
43. Goodwin T, Delasobera BE, Fisher PG. Reproductive health issues in survivors of childhood and adult brain tumors. *Cancer Treat Res*. 2009;150:215–22.
44. Farrell PC, Richards G. Recognition and treatment of sleep-disordered breathing: an important component of chronic disease management. *J Transl Med*. 2017;15:114.
45. Armstrong GT, Jain N, Liu W, Merchant TE, Stovall M, Srivastava DK, et al. Region-specific radiotherapy and neuropsychological outcomes in adult survivors of childhood CNS malignancies. *Neuro-Oncology*. 2010;12:1173–86.
46. Wells EM, Ullrich NJ, Seidel K, Leisenring W, Sklar CA, Armstrong GT, et al. Longitudinal assessment of late-onset neurologic conditions in survivors of childhood central nervous system tumors: a Childhood Cancer Survivor Study report. *Neuro-Oncol*. 2018;20:132–42
- Serial probing of the Childhood Cancer Survivor Cohort demonstrated that adult survivors of childhood brain tumors remain at risk for new onset neurologic events across their lifespan at a rate greater than siblings.
47. Netson KL, Ashford, Skinner T, Carty, Wu S, Merchant TE, et al. Executive function is associated with poorer health related quality of life in pediatric brain tumor survivors. *J Neuro-oncology*. 2016;128:313–21.
48. Neu MA, Tanyildizi Y, Wingerter A, Henninger N, Malki KE, Alt F, et al. Susceptibility-weighted magnetic resonance imaging of cerebrovascular sequelae after radiotherapy for pediatric brain tumors. *Radiother Oncol*. 2018;127:280–6.
49. Wang C, Roberts KB, Bindra RS, Chiang VL, Yu JB. Delayed cerebral vasculopathy following cranial radiation therapy for pediatric tumors. *Pediatr Neurol*. 2014;50:549–56.
50. Duat-Rodriguez A, Carceller Lechon F, Lopez Pino MA, Rodreguez Fernandez C, Gonzalez-Gutierrez-Solana L. Neurofibromatosis type 1 associated with moyamoya syndrome in children. *Pediatr Neurol*. 2014;50:96–8.
51. Brinkman TA, Bass JK, Li Z, Ness KK, Gajjar A, Pappo AS, et al. Treatment induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: results from the St. Jude Lifetime Cohort Study. *Cancer*. 2015;121:4053–61.
52. Brinkman TM, Ness KK, Li Z, Huang IC, Krull KR, Gajjar A, et al. Attainment of functional and social independence in adult survivors of pediatric CNS tumors: a report from the St Jude Lifetime Cohort Study. *J Clin Oncol*. 2018;36:2762–9.
53. Iyer NS, Balsamo LM, Bracken MB, Kadan-Lottick NS. Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: a review and eta-analysis. *Blood*. 2015;13:346–53.
54. Ness KK, Armstrong GT, Kundu M, Wilson CL, Tchkonja T, Kirkland JL. Frailty in childhood cancer survivors. *Cancer*. 2015;121:1540–7.
55. Ness KK, Kirkland JL, Graatges MM, Wang Z, Kundu M, McCastlain K, et al. Premature physiologic aging as a paradigm for understanding increased risk of adverse health across the lifespan of survivors of childhood cancer. *J Clin Oncol*. 2018;36:2206–15.
56. Sutradhar R, Agha M, Pole JD, Greenberg M, Guttmann A, Hodgson D, et al. Specialized survivor clinic attendance is associated with decreased rates of emergency department visits in adult survivors of childhood cancer. *Cancer*. 2015;121:4389–97.
57. Kadan-Lottick NS, Ross WL, Mitchell HR, Rotatori J, Gros CP, Ma X. Randomized trial of the impact of empowering childhood cancer survivors with survivorship care plans. *J Natl Cancer inst*. 2018;110:1352–1359.