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Surveillance of long-term complications after treatment of adult brain tumor survivors—review and evidence-based recommendations

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Abstract

As a result of treatment and diagnosis, adults with primary or metastatic brain tumors experience comorbidities that impacts their health and well-being. The Children's Oncology Group has guideline recommendations for childhood survivors of brain tumors; however, guidelines for monitoring long-term sequela among adult brain tumor survivors are lacking. The purpose of this review is to present the screening recommendations for the long-term complications after brain tumor treatment from a multidisciplinary panel of healthcare professionals. Chronic complications identified include cognitive dysfunction, vasculopathy, endocrinopathy, ophthalmic, ototoxicity, physical disability, sleep disturbance, mood disorder, unemployment, financial toxicity, and secondary malignancy. We invited specialists across disciplines to perform a literature search and provide expert recommendations for surveillance for long-term complications for adult brain tumor survivors. The Brain Tumor Center Survivorship Committee recommends routine screening using laboratory testing, subjective assessment of symptoms, and objective evaluations to appropriately monitor the complications of brain tumor treatments. Effective monitoring and treatment should involve collaboration with primary care providers and may require referral to other specialties and support services to provide patient-centered care during neuro-oncology survivorship. Further research is necessary to document the incidence and prevalence of medical complications as well as evaluate the efficacy of screening and neuro-oncology survivorship programs.

Keywords

adults | brain tumor survivorship | long-term complications | management | toxicity

Annually 88 000 adults are diagnosed with primary benign or malignant brain tumors and over 200 000 patients with secondary or metastatic brain tumors.[1] Surgery, radiation therapy (RT), and chemotherapy (CTX) are necessary treatments to prevent neurological deterioration and extend overall survival for patients with brain tumors. With improved survival, especially among adults with metastatic BT, more survivors may experience chronic symptoms, comorbidities, and psychosocial issues that impact their overall well-being, daily functioning, and quality of life (QOL). Commonly identified complications among BT survivors include cognitive dysfunction, vasculopathy, endocrinopathy, ophthalmic sequela, ototoxicity, physical disability, sleep disturbance, mood disorder, unemployment, financial toxicity, secondary malignancy, and care partner fatigue. While there are guidelines for childhood survivors of BT, there are limited guidelines for screening, monitoring, and managing treatment-related complications for individuals diagnosed as adults with BT. This review aims to present the results of the literature review and expert recommendations from a multidisciplinary panel of healthcare professionals for assessing and screening for complications of treatment during adult neuro-oncology survivorship.

Methods

A multidisciplinary committee composed of physicians, advanced practice providers, nurses, rehabilitation counselors, clinical psychologists, social workers, audiologists, and neuropsychologists was assembled. The committee focused on patients diagnosed with intracranial BT diagnosed as adults (age 18 or older). Adult complications of spinal cord tumors and spinal cord radiation or surgery are beyond the scope of this work.

The committee reviewed the National Comprehensive Cancer Network (NCCN)[2] and Children's Oncology Group Guideline[3] to provide a foundation for a focused literature review. The databases used during the literature review were PubMed, EMBASE, and CINAHL. The committee structured literature review and meetings based on the COG guidelines to review possible complications for adult BT survivors. To bridge the literature gap in the adult screening, experts in the adult specialties in radiation oncology, neuropsychology, endocrinology, vascular neurology, otolaryngology, ophthalmology, sleep medicine, and rehabilitation medicine were invited to discuss their perspectives and recommendations on the screening and management of BT survivors. When multiple screening tools were available, the committee discussed the quality of the literature, clinical availability of the tool, and patient response burden to develop the suggested recommendations. Detailed transcriptions were gathered from these meetings and used by committee members to summarize the recommendations in the following sections.

Cognitive Function

Cognitive dysfunction is the most common neurologic symptom in adult patients with primary or metastatic BT; however, the NCCN guidelines do not suggest screening methods in patients with CNS malignancies.[2] The majority of patients with primary BT have cognitive impairment in multiple domains at the time of tumor discovery.[4] Tumor location and characteristics may determine the type of cognitive symptoms, often caused by compression of brain structures, edema, and/or disruption of neural circuitry. Additionally, patient attributes (e.g., age, cognitive reserve, medical and psychiatric histories) modulate cognitive symptom onset and severity. Brain-directed treatments and other co-occurring factors (eg, seizures, medications, cerebrovascular disease, and medical/psychiatric conditions) also contribute to cognitive dysfunction. Memory, executive functioning, and processing speed commonly impact patient functional status more than any BT-related symptom.[5]

Response biases can skew patient reports (eg, deficit unawareness), resulting in under- or over-endorsement of cognitive symptoms; thus, cognitive assessment requires a combination of patient-reported, observer-reported, and performance-based strategies. A thoroughly conducted interview allows for ascertaining detailed baseline historical, medical, developmental, and psychosocial factors influencing the patient's cognitive status. Inclusion of the care partners' observation is beneficial as collateral information to provide additional insight into reported cognitive symptoms.

Psychometric instruments such as the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT),[6] Functional Assessment of Cancer Therapy—Cognitive (FACT-Cog),[7] and FACT—Brain Tumor[8] have been explicitly developed for tumor treatment outcomes to provide information on the presence of cognitive symptoms and their effects on functional status.

Brief cognitive screening instruments offer a standardized way of monitoring the presence, severity, and trends of cognitive dysfunction throughout the disease trajectory. Cognitive screening tools used in BT patients, including the Montreal Cognitive Assessment (MoCA), Clinical Trial Battery, and the computer-based CNS Vital Signs, have been explored in BT outcomes research. Only the MoCA is widely available for use in clinical practice.

Screening instruments can lack sufficient sensitivity in detecting cognitive symptoms, especially if mild in severity.[9] Neuropsychological evaluation (NPE) is a more comprehensive, tailored assessment of cognitive symptoms. NPE, while providing greater sensitivity and scope, is resource-intensive in terms of testing time, materials, and appropriate expertise (eg, neuropsychologist) in test administration and test score interpretation. Its incremental value in clinical management increases with time over the disease course, with more comprehensive evaluation particularly useful in differentiating co-occurring contributory factors, informing treatment recommendations, and determining readiness to return to activities such as employment and school.

Our group recommends routine screening of subjective and objective cognitive functions to evaluate the change over time and help guide additional evaluations or interventions (See Table 1). NPE can identify domains of impairments and help to guide cognitive rehabilitation, emphasizing compensatory-based treatment.[10]

Suggested recommendation:

Table 1. Suggested Screening for cognitive impairment

Ideal Patient Screening	Brief Patient Screening	Potential Contributing Factors
Subjective: MDASI – BT FACT – Cog FACT – BT Objective: NPE	Subjective: Have you noted any changes in your thinking? Have family members expressed any personality or behavioral concerns? Objective: FACT – BT	Medication side effects Emotional distress Symptoms: Pain, fatigue, sleep disturbance Use of alcohol or other agents that alter cognition Screening endocrinopathies Vitamin deficiencies (B1, B12, D)

- Cognitive screening every 6–12 months from the time of BT diagnosis with:
  - Montreal Cognitive Assessment (MoCA) or other cognitive screening tools.
  - Patient-reported symptoms and care partner's observations.
- If cognitive impairment is identified, evaluation of potential contributing factors and consideration for NPE and cognitive rehabilitation.

Cerebrovascular Complications

Cerebrovascular disease is a known long-term complication of BT treatments, secondary to RT and CTX. RT-induced complications include stroke, moya-moya disease, occlusive vasculopathy, cavernomas, and Stroke-like migraine attacks after RT (SMART syndrome). Risk factors for vasculopathy[11,12] are summarized in Table 2. RT-induced vasculopathy predominantly affects larger arteries, such as the internal carotid arteries and Circle of Willis.[13] Small vessel involvement is also well documented clinically by both ischemic and hemorrhagic stroke or radiographically by microbleeds and white matter hyperintensity. The time from treatment to the development of cerebrovascular complications in adults varies widely and is likely impacted by pre-existing cerebrovascular disease. In one series, the reported median interval between completion of RT to stroke was 3.2 years; however, the range was 0.5–30 years.[14] Small vessel changes, including lacunar infarcts and progressive white matter hyperintensity, occur earlier (<6 months) than large vessel stroke.[15]

Given the risk of vasculopathy, optimization of reversible vascular risk factors (diabetes, hypertension, etc.) is recommended for BT survivors treated with cranial RT. Vascular imaging should be considered among high-risk individuals and those presenting symptoms (ie, TIA, stroke, and amaurosis fugax) to assess vascular flow and secondary lesions. The ideal option for intracranial large vessel imaging is the ventricular mass index (VMI)—MRI, which gives high-resolution pictures of the vessel wall compared to the Carotid-Intima Media Thickness test (CIMT).[16] If VMI-MRI is unavailable, a CTA head is preferred over standard magnetic resonance angiography (MRA) head for intracranial large vessel evaluation, renal function permitting. Vasculopathy affecting small vessels occur rather acutely due to abundant endothelial cells, which are extremely sensitive to RT.[17] Unfortunately, these small vessels cannot be imaged with available technology. Structural brain MRIs can identify chronic small vessel ischemia areas as lacune orT2 hyperintensity. It is well understood that vasculopathy risk may accumulate over time. Clinical or imaging evidence of vasculopathy or ischemia should prompt referral to a vascular neurologist for evaluation and treatment.

The cerebrovascular risks from CTX during active treatment are related to endothelial toxicity and abnormalities in coagulation and hemostasis factors.[18] Stroke-like events and stroke have been reported after methotrexate treatment, with a 40-fold increase among long-term survivors from pediatric cancer groups.[19,20] This group does not recommend screening BT survivors treated alone with chemotherapy, immunotherapy, or targeted agents, as most known cases occur in the acute setting during treatment, and incidence in survivorship is rare.

Suggested recommendation:

- Management of vascular risk factors treated with cranial RT.
- Consideration of vascular imaging among high-risk individuals and those presenting symptoms.
- If there is evidence of vasculopathy by vessel imaging or clinical presentation, patients should be referred to a vascular neurologist for further evaluation and management.

Endocrinopathy

BT survivors are at risk for endocrinopathies related to the BT, surgery, RT, CTX, and other medications. The timing of the onset and type of endocrinopathy is related to the location and kind of BT and the treatment modalities employed. Most endocrinopathies are related to direct and indirect effects on the functioning of the hypothalamic-pituitary-end-organ axis. However, CTX can directly affect the gonads, leading to primary hypogonadism and infertility.[21,22] Corticosteroids, frequently used in patients with BT, can also result in pituitary dysfunction. Although the effects are reversible if the corticosteroids are withdrawn, even relatively short-term use can have long-term adverse effects on obesity, insulin resistance, and the subsequent risk of diabetes and osteoporosis. More recently, the increasing use of immune checkpoint inhibitors (ICI) has led to a diverse list of immune-mediated endocrinopathies that may be secondary (pituitary) or primary (end-organ) in etiology resulting in specific endocrine surveillance guidelines.[23]

Tumors and surgical procedures that involve the hypothalamus or pituitary are likely to result in endocrine dysfunction in the short-term. However, retrospective data have also

Table 2. Cerebrovascular Risk Factors, Screening Among Adult Brain Tumor Survivors

High-risk factors
RT to sellar/parasellar, prepontine cistern, posterior fossa
RT dose ≥ 50 Gy
Age > 55
Genetic risk factors (eg, neurofibromatosis type 1)
Concomitant chemotherapy (eg, cisplatin)
Extent of RT fields
Suggested screening recommendation
Small vessel
MRI brain (containing a minimum of T2, T2 Flair, T1 and DWI/ADC sequences)
High risk: consideration of screening of imaging at year 1, 3, and then 5-year intervals from the time of radiation.
Large vessel: intracranial (occlusive vasculopathy as well as aneurysm
High-resolution VWI-MRI head is preferred every 3–5 years based on imaging and clinical factors. If VWI-MRI is not available consider CTA head or MRA head
High risk: consideration of vessel imaging at 1, 3, and 5 years after RT and continue every 5 years if no vasculopathy is identified
Secondary vascular pathology (cavernomas, microhemorrhages)
Cavernomas and microhemorrhages: consideration of including T2* imaging (ex: GRE, SWI) at least every 5 years
Management
Vasculopathy
Referral to vascular neurology for consideration of antiplatelet agents and secondary stroke risk factor modification.
Moderate aerobic exercise 30 min 3–4 times a week

demonstrated delayed pituitary dysfunction after surgical intervention, even when BT is distant from the pituitary and hypothalamus.[24] The effects of cranial RT on the endocrine systems may be undetected, given that symptoms of endocrine dysfunction can be subtle, non-specific, and gradual in onset. While the risk correlates with the RT dose to the hypothalamus and less so to the pituitary, the overall incidence of RT-induced pituitary dysfunction for tumors distant from the pituitary range from 38% to 80%.[23,25] Endocrine deficiencies may occur as early as three months or greater than ten years after RT or neurosurgical procedures.[26] Deficiencies of growth hormone, gonadotropins, thyroid-stimulating hormone, and adrenocorticotropin (ACTH) can occur singly or in combinations.

Our group recommends yearly screening of pituitary function, including thyroid and ACTH deficiency. TSH alone is insufficient to screen for thyroid dysfunction and requires free T4 in patients who received brain RT. Adrenal insufficiency can be a life-threatening condition and is diagnosed by the "gold standard" cosyntropin stimulation test. However, an AM cortisol value > 13 ug/dl is reassuring for normal function.[27] Those with abnormal values should be referred to endocrinology for formal evaluation. Additionally, screening for pituitary deficiencies should be done whenever there is clinical suspicion, regardless of prior treatment. Growth hormone deficiency has great importance in children but can also be a factor in determining QOL issues in adults. Deficiencies of sex steroids can have wide-ranging effects, including an increased risk of osteoporosis. Our group recommends screening for testosterone and estrogen as clinically indicated. These recommendations are also summarized in Table 3.

Suggested recommendation:

- For patients treated with brain RT, annual screening of pituitary function with TSH, free T4, and morning cortisol.
- Estrogen and testosterone screening may be considered as clinically indicated.

Ophthalmic Sequelae

Considerations of ocular pathology in the setting of BT survivors are dependent not only on the type and location of the BT but also on accompanied treatment modalities. Preoperative counseling and expectation management are imperative given the poor potential of vision recovery after insult. While local compression and/or resection of BT are often the main source of morbidity in this patient population, RT and CTX have risks of ocular toxicity.[28–30] Table 4 summarizes ophthalmic complications commonly observed in BT survivors. Lastly, ICI medications also have possible ocular side effects, including retinal and optic nerve toxicity, anterior uveitis, and myasthenia gravis.[31] These reactions are exceedingly rare, less than 1%; however, they should be considered ocular manifestations that can occur 1 week to 52 weeks from starting ICI.[32] Collaboration and routine follow-up with ophthalmology specialists are essential to minimize ocular toxicity post-treatment during survivorship.

Suggested recommendation:

- For those who underwent cranial RT or have known ophthalmic BT sequela, perform an annual vision examination with consideration of referral to neuro-ophthalmology/ophthalmology.

Table 3. Suggested Adult Brain Tumor Survivorship Guideline

Complication	Brain Tumor Treatment	Suggested Screening Recommendations	Frequency
Eye	Cranial radiation close to optic nerve or known ocular pathology related to tumor or treatment	Neuro-ophthalmology evaluation	Annually
	All brain tumor	Comprehensive eye examination	Every 1-2 years
Hearing	All brain tumor	Hearing screen question: Do you have any difficulty with hearing?	Annually
	Patients with cisplatin >200 mg/m^2 or carboplatin >1500 mg/m^2	Audiology testing	Post treatment, 2 years after, then every 5 years
	Patient with Cranial RT	Post treatment baseline with audiogram. If detected hearing loss, annual audiogram. If normal, proceed with survey screening annually as below.	Annually
	Radiosurgery near CN VIII	Audiology testing	Annually
Cognition	Any	MoCA	Every 6 -12 months
Hormones/Endocrine	All brain tumor	Annual survey for symptoms	Every 6 -12 months
	Brain Radiation	TSH, freeT4, AM cortisol Men –Testosterone Women of child-bearing age – clinic screening with question of experiencing irregular menses	Annually
	Immunotherapy	Per NCCN guidelines	Per NCCN guidelines
	Chemotherapy	Men: Testosterone Women of child-bearing age – clinic screening with question of experiencing irregular menses	Men: Test once post treatment Women: Annually
Mood	Any	PHQ9 and GAD	Every 6 months
Sleep	Any	Insomnia single question: Do you have problems falling sleep or staying asleep for three or more nights per week?	Annually
		STOP BANG	Every 5 years
		RLS single question: "When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?"	Annually
Balance/ Coordination	Any	Survey questions and exam: Have you had any difficulty taking care of yourself, walking, balancing, or falling? Have you had any difficulty taking your own medications?	Annually
		Tandem stance (5-10 seconds), Romberg, Single leg stance	Annually
Cerebrovascular	Brain Radiation	Brain Vessel Imaging (CTA vs MRI)	1 year from XRT, then 3 years. If no vasculopathy every 5 years. If cardiovascular risk factors every 3 years.
		MRI brain with T2* imaging	Every 5 years
Employment	Any	If you are currently in work or school: Are you having difficulty preforming tasks at work or school? How often are you missing work? Have you received negative feedback on job/school performance? Is it taking you longer to complete tasks? Are you behind at work or putting in extra hours to keep up? Do you have concerns your employment or enrollment are in jeopardy?	Every 6 months
Financial	Any	Over the last 6 months: Are you feeling more financially stressed? Are you struggling to meet monthly expenses?	Every 6 months

Table 3. Continued

Complication	Brain Tumor Treatment	Suggested Screening Recommendations	Frequency
Support/Caregivers	Any	Subjective Assessment/Survey Clinical Screening: Caregiver Needs Screen in Neuro-Oncology Family Caregivers (CNS) Distress Thermometer Kingston Caregiver Stress Scale (KCSS)	Every 6 months
Secondary Malignancy	Chemotherapy or XRT	Physical exam	Annually

Ototoxicity

Adult BT survivors experience ototoxicity as tinnitus and/or progressive, irreversible hearing loss. Ototoxicity is a common complication of platinum CTX and cranial RT, with more than 50% of patients who receive a combined modality developing treatment-induced hearing loss.[33] However, this prevalence varies depending on the treatment regimen, patient age, baseline hearing levels, the presence of other confounding factors such as co-medications, renal toxicity, concomitant noise exposure, and genetic susceptibility.[34] Hearing loss affects speech recognition and ease of communication; thus is associated with increased stress, social isolation, loneliness, impaired memory and cognition, and risk for dementia.[35] Early identification of hearing loss and rehabilitation is crucial as it reduces the negative impacts on communication, QOL, and influences cognitive rehabilitation.[36]

Our group recommends long-term surveillance due to the risk of progressive hearing loss for any BT survivor treated with cranial RT or ototoxic chemotherapy. While audiology screening is the standard of care for children treated with ototoxic therapy, most adults with cancer do not receive baseline or post-treatment hearing evaluations.[38] Survivorship programs provide an essential opportunity to address unmet hearing needs for patients who received ototoxic cancer therapy.

Suggested recommendation:

- For patients who received cisplatin > 200 mg/m^2, carboplatin > 1500 mg/m^2, formal hearing evaluation post-treatment, two years, and every 5 years.
- For patients treated with posterior fossa stereotactic radiosurgery (SRS), especially around the 8th cranial nerve, audiology screening post-treatment followed by annual testing.
- For patients who received cranial RT of 30 Gy or greater, baseline audiogram after treatment, if normal annual survey screening.
- Audiology and otolaryngology consultation for ongoing hearing surveillance for any BT survivor who has symptoms of hearing loss, tinnitus, or an abnormal hearing screen.

Physical Function

Impaired physical functioning, such as weakness, gait, and balance disorders, are prevalent in greater than 50% of BT survivors.[36,37] gait and balance disorders are multifactorial due to the primary tumor, surgical resection, and/or treatment sequelae. Our group recommends a comprehensive neurological evaluation combined with questions focused on functioning during routine surveillance since a decline in physical functioning affects QOL and individuals' risk for falls or injury (see Table 5). Gait speed measured with the 10-m walk test (10MWT) can be performed in the clinic to help identify patients at elevated risk for falls (speed cut-off < 0.7 m/s).[38] Increased difficulty in performing activities of daily living or medication management is also indicative of possible BT-related sequelae. Routine evaluation of gait, balance, and physical functioning can detect subtle changes that could indicate tumor recurrence, new or worsening hydrocephalus, or late-delayed RT effects that may require medical interventions.[41] Careful review of brain imaging to evaluate underlying structural causes with any change in function. Once the diagnostic workup is completed, we recommend referral to rehabilitation services. Patients with drastic changes in function or worsening spasticity should be referred to a physiatrist for a comprehensive evaluation, treatment, and rehabilitation therapy management.

Suggested recommendation:

- For all BT survivors, annual subjective assessment of independence and mobility.
- For all BT survivors, annual comprehensive neurological examination evaluating strength, coordination, vision, balance, tone, and cerebellar signs.

Sleep Disturbance

Sleep disturbance is one of the most commonly reported symptoms among patients with BT. Sleep disturbance, in this review, is the perceived or actual alterations in sleep resulting in impaired daytime functioning. Sleep disturbance encompasses insomnia, sleep-related breathing such as Obstructive Sleep Apnea (OSA), movement disorders like restless legs syndrome (RLS), and dissatisfaction with sleep quality. Because of its close association with psychological well-being, cognitive functioning, and QOL,[39] our group recommends routine screening of sleep issues. The proposed sleep disturbance screening algorithm is described in Figure 1. The questionnaires included in the algorithm have shown sensitivity in neuro-oncology literature.[45] Insomnia Severity Index (ISI) is a relatively short 7-question instrument that has demonstrated validity and internal consistency in cancer patients, including BT survivors. While a single cut-off for clinically significant

Table 4. Summary of Ophthalmic Sequela in Adult Brain Tumor Survivors

Complication	Manifestation
Visual field defect: Any damage along the posterior visual pathway may result in a contralateral homonymous visual defect	Patients typically complain of vision loss, often just in the eye with the temporal visual field loss, although they may present with difficulty reading or navigating
Optic neuropathy: Local compression/edema may acutely lead to optic nerve injury	Decreased vision, dyschromatopsia, and visual field loss
Cranial nerve palsy (III, IV, and VI)	Binocular diplopia is the most common complaint
Dry eye syndrome: Dose-dependent; exposure of ~34 Gy cumulative radiation carries a ~5% risk of severe DES	Complaints of foreign body sensation, stinging/burning eye pain, blurry vision worsened with reading or visual tasks
Cataract: Dose-dependent, risk increases with as little ~2–5 Gy in one fraction	Patients will complain of gradual decreased visual acuity or glare
Radiation retinopathy: Dose-dependent; exposure to less than ~25 Gy cumulative radiation is unlikely to develop significant retinopathy	Patients typically complain of gradual decreased visual acuity
Radiation optic neuropathy: Radiation doses from 50 to 60 Gy assumes a risk of ~5% within 10 years	Characterized by painless, progressive, rapid vision loss/dyschromatopsia over several days to weeks. May present acutely or years post-exposure (peak incidence 1.5 years)

insomnia has not been reported in BT survivors, data was extrapolated from other cancer types. If the ISI score is greater than 15, discussion of pharmacologic treatment and non-pharmacologic treatment with their PCP or referral to a sleep specialist is advised.[40,41] Lastly, multiple studies have found an association between OSA and malignant BT.[42,43] Given the health consequences of untreated OSA, it is prudent to include screening for OSA using the well-validated STOP-BANG tool every five years, regardless of sleep disturbance.

Suggested recommendation:

- Annual screening from the time of BT diagnosis, independent of treatment, using ISI.
- STOP-BANG questionnaire screening every five years to screen for OSA.

Mood

Clinically important symptoms of depression, anxiety, and suicidal ideation are common complications that adversely affect patients with BT.[44–46] Depression rates in survivors of BT are among the highest compared to survivors of other cancers.[45] Within the first year of survivorship, the prevalence of depression among BT survivors ranges from 15% to 28%, with higher rates among patients with glioma.[44,45,47] After treatment, the prevalence of depression increases to 38–42% and anxiety to 48%, with comorbid depression and anxiety at 31–34%.[46] Suicidal ideation, reported in 10–12% of BT survivors, is associated with depression and anxiety severity, history of psychiatric disorders, and poorer health-related QOL.[48] Other long-term side effects, including sleep disturbance, fatigue, and cognitive deficits overlap with depression and anxiety.[49–51] Thus, careful evaluation is required to determine whether an underlying mood disorder is present and requires treatment.

The etiology of mood problems in BT survivors is multifactorial and can be influenced by tumor location, treatment, medications (eg, antiepileptic therapy, corticosteroid use), adjustment-related distress in response to the diagnosis, prognosis, and social and environmental factors (eg, family psychiatric history).[47] Anxiety and depression symptoms are closely associated with diminished QOL, worse survival outcomes, and complications, such as deep vein thrombosis, seizure, systemic infection, and adverse drug reactions.[44,49–51] Thus, our group recommends screening for these symptoms at the time of diagnosis, throughout the disease trajectory, and every six months into survivorship to inform appropriate treatment and mental health care. This screening can often be done in partnership with their PCP, given United States Preventive Services Task Force guidelines for screening all adults.[52] Standard self-report measures such as Hospital Anxiety and Depressional Scale (HADS),[53] 9-item Patient Health Questionnaire (PHQ-9),[54] and a 7-item Generalized Anxiety Disorder (GAD-7)[55] have been used in cancer survivors, including BT survivors, to screen for depression and anxiety symptoms. A score of ≥ 7 on the HADS depression subscale[56,57] and ≥ 8 on the HADS anxiety subscale,[53] or a score of ≥ 10 on the PHQ-9[56,57] or GAD -7[58] warrant further investigation for a mood disorder.

Suggested recommendation:

- Routine screening at the time of diagnosis, then every six months using validated measures such as PHQ-9 and GAD-7 for all BT patients in partnership with PCP.
- Referrals to mental health specialists for further evaluation and interventions.

Financial Toxicity and Employment Status

The economic burden of BT survivors accumulates during their cancer diagnosis trajectory. The cost of treatment is estimated to be as high as $138 767 for those who received both CTX and RT, with a cumulative cost ranging from $262 877 to $274 416 at five years.[59] Contributing factors to financial toxicity involve high unemployment and loss of income from the patient and their informal care partner, insurance reimbursement with large segments of out-of-pocket from medications/durable medical equipment, and medical expenses for hospital/physician services.[60,61] Furthermore,

Table 5. Summary of Proposed Evaluation and Recommendation in Physical Function

Subjective Questionnaire: In The Past Three Months, Have You Had Difficulty With	Specific Exam Maneuver	Referral Services as Indicated by Subjective and/or Physical Exam
Taking care of yourself (bathing, toileting, dressing)?	See the cognitive function section, strength testing, and balance testing as below	Occupational therapy
Walking, balancing, or falling?	Tandem stance < 10 s or single leg stance < 5 s, visuospatial neglect (letter cancellation test), 10MWT (gait speed < 0.7 m/s)	Physiatry (physical medicine and rehabilitation) and/or physical therapy
Taking medications without assistance?	Fine motor coordination in addition to cognitive screening.	Occupational therapy (fine/gross motor coordination, functional cognition) and/or speech therapy (swallow and/or cognitive therapy)

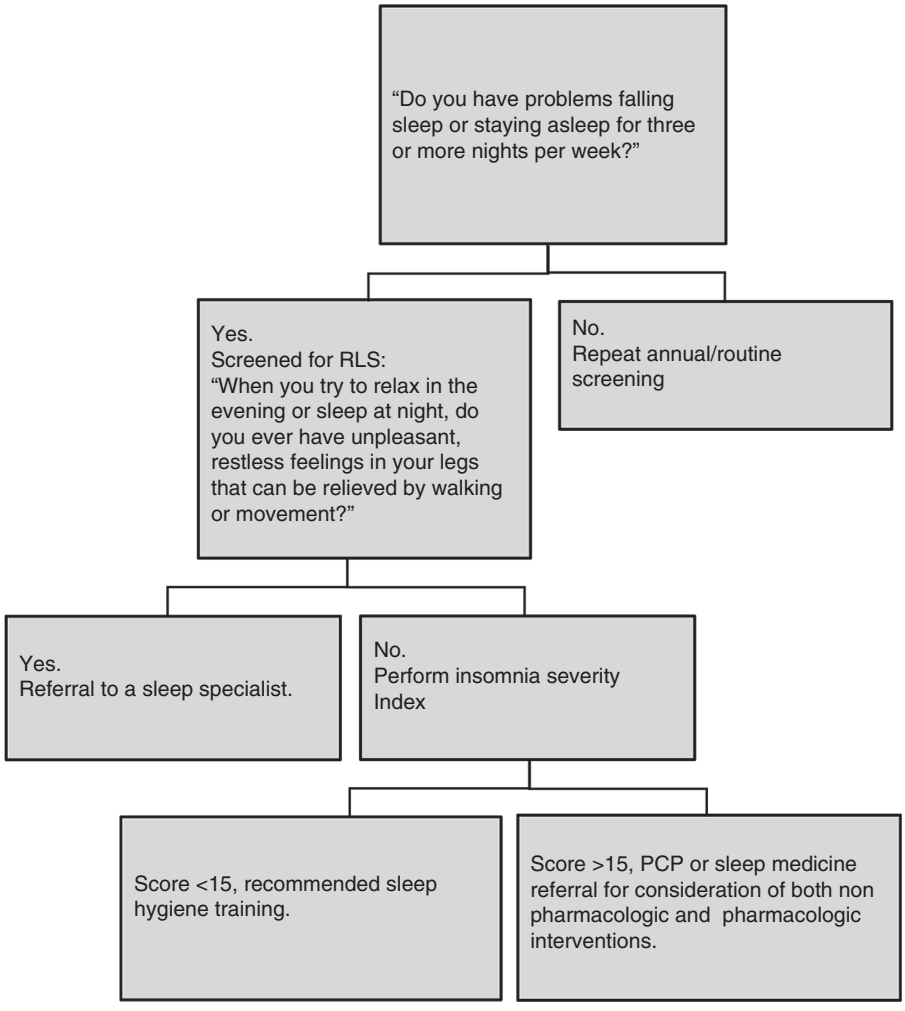

Figure 1. Algorithm of sleep disturbance screening and surveillance.

the cost of transportation, home care services, and childcare potentiate this financial crisis resulting in acquiring loans in approximately 25–50% of patients.[61] Our group recommends screening, assessing, evaluating, and managing financial toxicity as financial burden impacts overall survival, symptom burden, and QOL of cancer survivors.

We suggest screening by asking if they are experiencing medical financial hardship. If so, this is followed by a collaboration with patient navigators, social workers, or providers in assessing and adjusting the current treatment plan and identifying resources for financial assistance.[62]

Assessing employment status and successful return to work is crucial in maintaining financial stability long-term. Employment is a valuable contributor to QOL, maintenance of identity, and physical and emotional health. In addition to providing financial security, employment for many BT survivors is necessary for accessing essential healthcare benefits.

BT survivors are at risk of employment disruption and job loss due to the impact of treatment and disease-related symptoms on work capacity.[63] Decreased productivity, absenteeism, and job performance problems can occur, with fatigue and cognitive impairment as key symptoms leading to job challenges.[63] Patients often under-report employment problems; therefore, our group recommends explicitly asking if they have any difficulty performing job duties or how often they are missing work (Table 3). Educating patients about disability rights, developing employment support strategies, and referral to Vocational Rehabilitation (VR) are fundamental parts of survivorship counseling. VR can facilitate services for individuals with disabilities that have difficulty maintaining employment or returning to work through job accommodation and modification, employment retention, and funding for job training, equipment, and other medical services.

Suggested recommendation:

- Subjective assessment of medical financial hardship at the time of tumor diagnosis and every six months for all BT patients.
- Collaboration between social workers, patient navigators, and providers in adjusting the current treatment plan and identifying resources for financial assistance.
- Subjective assessment of employment status, productivity, and absenteeism every six months and early referral to vocational rehabilitation.

Caregiver Burden and Support

Care partners must monitor and often mitigate debilitating physiological, behavioral, and cognitive symptoms of BT survivors. Although caregiving can be very fulfilling, it is demanding and stressful, especially when care partners have multiple competing responsibilities and care recipients have unmet care needs.[64] Hence, most BT care partners experience significant distress.[65] Caregiving demands may influence partner's physical and emotional health, their ability to provide care, and even the recipient's survival.[66,67] It is imperative that clinicians regularly assess and address care partner needs. Best practices for supporting BT patients include frequent monitoring using patient-reported outcome measures and tailored supportive care. Our group recommends the same practices for care partners. Because caregivers are not patients of record, most health systems do not have the efficient infrastructure and trained staff to ensure that their needs are regularly reflected in care plans.

Assessment measures developed for general cancer populations do not capture neurological and cognitive difficulties. They, therefore, have limited generalizability to BT patients. Caregiver Needs Screen in Neuro-Oncology Family Caregivers [CNS][68] is one of the best disease-specific validated measures. CNS is a 30-item, participant-centered self-report that takes 5–7 min to administer. Other measures applicable in neuro-oncology are caregiver needs assessments developed for people living with dementia. A comprehensive review of the reliability, validity, and relevance of these measures identified Partnering for Better Health: Living with Dementia [PBH-LCI][69] as a current gold standard.[70] Furthermore, most BT care partners report higher distress than their care recipients but do not endorse these symptoms spontaneously. We recommend that clinicians must iteratively assess and address caregiver stress.[71,72] Clinic visits are usually very taxing and not an indicator of overall stress.[64] The best measurement approach is to prompt caregivers to reflect on their stress levels during the past week at home. A distress thermometer is a gold standard measure of stress in oncology. Another practical measure is KCSS, a brief, valid, and reliable measure that assesses caregiving, family, and financial issues.[73] Care for BT survivors requires care partner support which includes educating clinicians about the importance of caregiver assessment[74] and, ideally, creating caregiver support programs and/or facilitating caregiver-to-caregiver peer support.[75]

Suggested recommendation:

- Subjective assessment of BT care partner's unmet needs and stress using Caregiver Needs Screen in Neuro-Oncology Family Caregivers (CNS), Distress Thermometer, or Kingston Caregiver Stress Scale (KCSS) at the time of tumor diagnosis and every 6 months.

Second Malignancy

BT survivors are at risk for secondary malignancies induced by ionizing RT. These can be detected several years after therapy within the radiation treatment field and differ in histology from the original tumor.[76] After brain irradiation, the most common secondary malignancy is meningioma, followed by glioma and sarcoma.[77–80] The precise incidence of secondary malignancy for adult BT survivors is challenging given the overall lack of long-term follow-up, ascertainment bias, and primary data concentration on the pediatric population. Secondary malignancies often develop away from the primary tumor location in the lower dose radiation regions. For instance, one study noted 12% of secondary malignancies in the irradiated volume (the planning target volume), 66% in the beam-bordering region, and 22% in the areas located more than 5 cm from the irradiated volume. There was no threshold dose for the risk of secondary malignancy.[81] The limited literature on the adult BT population, compared to the general population, suggests that the 30-year cumulative risk for secondary malignancy ranges from 2.7% to 8.5% in irradiated patients.[78,82–85] However, this incidence cannot be attributed to RT alone, as patients with primary BT already have an increased risk of subsequent secondary malignancy.[84,86]

Furthermore, most of the data on the adult population are from patients treated for pituitary adenoma with older RT techniques.[78,82,83] Current techniques allow for an overall decreased volume of the irradiated brain.

There is a paucity of data regarding whether early detection and surveillance for secondary malignancy improve outcomes.[87] Some studies suggest treatment can improve survival after secondary malignancy.[88] Thus, it may be helpful to detect secondary malignancy earlier. Our group recommends counseling on the risk of secondary malignancy, routine imaging surveillance as indicated for tumor surveillance or vasculopathy screening, and annual neurological exam. If a secondary malignancy is suspected, given varied RT techniques utilized, it is important to verify whether the secondary malignancy correlates with the irradiated field with the recorded treatment plan.

Suggested recommendation:

- Upfront counseling on the risk of secondary malignancy for BT patients at the time of cranial RT.
- Annual neurologic exam and routine imaging as indicated for tumor surveillance or vasculopathy screening.

Conclusion

As therapeutic and diagnostic strategies improve, especially for patients with metastatic brain tumors, the population of adult BT survivors will continue to grow. At this time, most BT survivorship research has focused on childhood survivors of primary BT, limiting the data to guide survivorship in adult BT survivors. We formed a multidisciplinary committee to review the available literature and develop recommendations for surveillance of adult BT survivors. These guidelines will advance future research into treatment complications in adult BT survivorship.

Our group recognizes the limitations of this review. There is an active project to evaluate care partners' and patients' perceptions regarding survivorship screening. The screening does require time and effort from patients and their care partners as well as medical providers. Optimal care of these complicated patients requires partnership with PCP as screening guidelines overlap with general health screening.[49] The majority of experts from this group were from a single-institution, and insurance coverage for screening at our institute has not been a barrier. A broader more diverse group of experts across the globe should be considered in revising these guidelines.

Despite the limitations of this review, comprehensive monitoring of the unique complications in adult BT survivors is necessary in addition to routine tumor surveillance. The comprehensive screening and surveillance recommendations developed through this multidisciplinary group are summarized in Table 3. On-going thorough symptom assessment during survivorship is required due to the variability of onset and progressive nature of the medical conditions. Recognition and early detection of treatment complications are intended to improve health and maximize the QOL of BT survivors. Further research is necessary to document the incidence and prevalence of medical complications as well as evaluate the efficacy of screening and neuro-oncology survivorship programs.

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