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Cardiac dysfunction in medulloblastoma survivors treated with photon irradiation

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Abstract

Background. Medulloblastoma is an aggressive central nervous system (CNS) tumor that occurs mostly in the pediatric population. Treatment often includes a combination of surgical resection, craniospinal irradiation (CSI), and chemotherapy. Children who receive standard photon CSI are at risk for cardiac toxicities including coronary artery disease, left ventricular scarring and dysfunction, valvular damage, and atherosclerosis. Current survivorship guidelines recommend routine echocardiogram (ECHO) surveillance. In this multi-institutional study, we describe markers of cardiac dysfunction in medulloblastoma survivors.

Methods. A retrospective chart review of medulloblastoma patients who had photon beam CSI was followed by ECHO between 1980 and 2010 at Lurie Children's Hospital and Dana-Farber/Boston Children's Hospital.

Results. During the 30-year study period, 168 medulloblastoma patient records were identified. Included in this study were the 75 patients who received CSI or spinal radiation and ECHO follow-up. The mean age at CSI was 8.6 years (range, 2.9-20), and the mean number of years between radiation therapy (RT) completion and first ECHO was 7.4 (range, 2-16). Mean ejection fraction (EF) was 60.0% and shortening fraction (SF) was 33.8%. Five patients (7%) had abnormal ECHO results: three with EF <50% and two with SF <28%.

Conclusion. The majority of medulloblastoma patients who received CSI have relatively normal ECHOs post-treatment; however, 7% of patients had abnormal ECHOs. The implication of our study for medulloblastoma survivors is that further investigations are needed in this population with a more systematic, longitudinal assessment to determine predictors and screenings.

Keywords

cardiac toxicity | ECHO surveillance | echocardiogram | pediatric brain tumor

Central nervous system (CNS) tumors are the most common solid tumors in children and the second most common pediatric malignancy after leukemia.[1,2] Mortality from high-grade CNS tumors is disproportionately greater compared to other childhood malignancies, and even low-grade tumors can be associated with significant morbidity.[3–5] The current therapeutic strategy—typically a combination of surgery, chemotherapy, and radiation therapy (RT)—poses a risk of cardiovascular complications. For example, the Childhood Cancer Cohort study found a 6-fold increased relative risk of myocardial infarction in childhood brain tumor survivors.[6] As survival rates for childhood cancer increase, this population becomes increasingly vulnerable to long-term therapy-related cardiac toxicities. As such, studies focusing on early management of these side effects are critical.

Cardiovascular side effects in pediatric cancer survivors manifest most commonly as pericardial disease—followed by coronary artery disease, cardiomyopathy, left ventricular

scarring and dysfunction, valvular abnormalities, and atherosclerosis.[6–13] While the drivers of therapy-induced cardiac toxicities can be multifactorial, the most common causes are RT with cardiac exposure and chemotherapy. Several studies in pediatric cancer survivor populations point to mediastinal/thoracic radiation (eg, for Hodgkin's disease and other mediastinal malignancies) as playing a significant role.[6,8,14] Cumulative doses of >30 Gy to the mediastinum/thoracic area are thought to contribute to cardiac damage.[14] Cardiac toxicity in adults who receive RT treatment during childhood is linked to radiation dose, as well as the fraction given and exposed heart volume.[6] It has been known that cumulative doses of >30 Gy radiation to the mediastinum/thoracic contribute to cardiac damage with further studies suggesting that lower doses (15-35 Gy) may result in damage to the coronary circulation.[6,14] The risks for different manifestations of cardiac disease are 2- to 6-fold higher when the cardiac RT dose exceeds 15 Gy.[7,13,14] Pediatric medulloblastoma patients treated with craniospinal irradiation (CSI) all receive spinal doses greater than 15 Gy, regardless of treatment protocol, with patients typically receiving 23-36 Gy in combination with chemotherapy. Doses to the heart vary, depending on the RT modality; but have been shown to result in doses to the heart that were approximately 50% and 28% of the spinal dose.[15,16] While the mechanistic underpinning of RT-induced cardiotoxicity is unclear, there is postulation that radiation induced inflammatory reactions, such as the release of tumor necrosis factor, interleukins, and transforming growth factor may result in diffuse interstitial fibrosis.[16,17]

In addition to RT, chemotherapy and targeted drug therapies can cause cardiotoxicity in survivors of childhood cancer—particularly anthracyclines, with cumulative lifetime doses of more than 300 mg/m^2 imparting the highest risk,[8,18] but also alkylating agents and targeted biological agents.[10,19,20] Anthracycline use is uncommon in the treatment of CNS tumors. Additionally, blood transfusions due to therapy-related anemia may contribute to cardiotoxicity by iron overload cardiomyopathy.[21–25]

In CNS tumor patients, there is direct cardiac damage from CSI-related scatter to the heart. Additionally, cranial RT exposure damages the hypothalamic-pituitary axis,[26,27] which can lead to growth hormone (GH) deficiency, often the first manifestation of hypopituitarism.[28,29] This can lead to changes in metabolism and/or hormone production that negatively impact obesity, lipid metabolism, insulin resistance, and diabetes mellitus[30–32]—thereby increasing cardiovascular risk.

Precisely because of these risks, a screening electrocardiogram (EKG) upon entry to into long-term follow-up, repeated as clinically indicated and serial echocardiogram (ECHO) (every 2-5 years) for monitoring left ventricular size and function has been included in the Children's Oncology Group (COG) Survivorship Guidelines since their inception in 2003. These guidelines were developed as a resource for healthcare providers to aid in screening late effects of therapy in asymptomatic survivors of childhood cancers. Risk factors (eg, radiation type and dose tumor location, and exposure to anthracyclines) are taken into consideration when establishing patient-specific follow-up screening plans. In this study, our objective was to retrospectively examine clinical records of pediatric medulloblastoma patients treated with CSI photon radiation and determine the incidence of cardiotoxicity.

Materials and Methods

A retrospective cohort study was conducted at Dana-Farber/Boston Children's Cancer and Blood Disorders Center and Lurie Children's Hospital. Both the Dana-Farber Cancer Institute and Lurie Children's Hospital IRBs approved this study.

Objectives

Data collected included demographics, details of medulloblastoma diagnosis and therapy, radiation dosing and field, and ECHO results.

Inclusion and exclusion criteria

Patients were (1) diagnosed with medulloblastoma between 1980 and 2010, (2) children (<21 years of age at diagnosis), (3) at least 2 years from the end of treatment, (4) received craniospinal or spinal photon beam radiation and had at least one ECHO post-treatment. Patients who received proton beam radiation were excluded.

Statistical analysis

Descriptive methods were used to present demographics, tumor histology, and age at diagnosis. Continuous variables were reported as mean, standard deviation, median, and ranges. Categorical variables were described by frequency and percentage. Adverse events were evaluated by chi-squared testing and adverse events over time by generalized estimating equations.

Results

During the study period (1980-2010), 168 patients were treated for medulloblastoma, 75 of whom had photon irradiation and ECHO follow-up and were therefore included in the study. Of the 75 patients, 73 were treated with CSI at diagnosis, one was treated with CSI at recurrence, and one with focal spinal RT. The mean age at CSI was 8.6 years (range, 2.9-20), and the median CSI dose was 23.4 Gy (range, 21.6-39.6) (Table 1). One patient received an additional 9 Gy boost to the spine (C6-S2/3), due to the presence of spinal disease. Two patients who initially received RT sparing treatment, subsequently received spine RT due to recurrent disease, doses at recurrence included 800 cGy focal to T9-10 and 36 Gy CSI. While one patient received only focal spine RT, the remainder (74 out of 75) received CSI: 35% were treated with 36 Gy to the spine and 63% with 21-35 Gy. Patients did not receive anthracyclines as part of their therapy.

Table 1. Characteristics of 75 Childhood Medulloblastoma Survivors

	No. of Cases (%)
Gender	
Male	33 (44)
Female	42 (56)
Medulloblastoma histological subtype	
Classic	30 (40)
Desmoplastic or nodular	10 (10)
Anaplastic or large cell	12 (16)
Unknown	23 (31)
Risk group	
Average	46 (61)
High	29 (39)
RT field	
CSI	75 (99)[a]
Focal RT only	1 (1)[b]
	Mean (range)
Age at CSI	8.6 (2.9-20)
ECHO	
Age at ECHO	15.6 (0.9-27)
Years post-RT at first ECHO	7.4 (2-16)
	Median (range), Gy
CSI dose	23.4 (21.6-39.6)
Total RT dose (CSI + boost)	54 (36-57.6)

Abbreviations: CSI, craniospinal irradiation; ECHO, echocardiogram; RT, radiation therapy.
[a]One patient was treated with RT sparing approach upfront and then with CSI at recurrence.
[b]Spinal focal RT.

Cardiac dysfunction

Most patients (80%; 60 out of 75) had one ECHO post-treatment, and the remainder (20%; 15 out of 75) had repeat cardiac testing. A minority (43%; 32 out of 75) of patients completed therapy prior to the implementation of the COG Survivorship Guidelines, but still had an ECHO performed following completion of therapy. The mean time post-CSI to first ECHO was 7.4 years (range, 2-16), and to second ECHO, when performed, was 11.9 years (range, 8.6-17.3). For the 4% (3/75) who received a third ECHO, the mean time post-RT was 12.6 years (range, 11.4-13.3).

Mean ejection fraction (EF) in the entire cohort was 60.0% and shortening fraction (SF) was 33.8%. Five patients (7%) had abnormal ECHO results ($P < 0.001$): three had EF <50%, and 2 had SF <28% (Table 2). All five patients were asymptomatic and treated with observation, with lifestyle changes suggested for two. Interestingly, four of the five patients with abnormal ECHOs were treated with lower dose irradiation (23.4 Gy CSI), whereas the fifth patient received 36 Gy CSI. Only two of the five patients with abnormal ECHOs had electrocardiograms (ECGs) performed, one of which was normal and the other demonstrated sinus tachycardia with a borderline prolonged QTc. Finally, one of the five patients had a cardiac MRI, which was normal.

Discussion

With improved survival in patients diagnosed with medulloblastoma over the past four decades, a great deal has been learned about long-term sequelae of treatment and, consequently, more attention has been directed at reducing these treatment-related late effects. By reviewing data from a large volume of patients seen in two pediatric neuro-oncology cancer survivorship programs, we show that 7% had abnormal ECHO findings, specifically abnormalities in EF or SF. Brain tumor survivors are at high risk for stroke, dyslipidemia, and obesity, and it is uncertain if these factors have a more profound long-term impact on their cardiac health as they age in comparison to the direct toxicity from radiation and chemotherapy. Further long-term cardiac investigations are needed in this population given that a small cohort of our patients had abnormal ECHO findings.

Although echocardiographic EF and SF have traditionally been used to monitor left ventricular systolic function, variation exists when alternative means, such as cardiovascular magnetic resonance (CMR) or gated single-photon emission computed tomography (SPECT) are used.[33] EF and SF may not reflect ventricular contractibility and instead are influenced by ventricular overload and afterload.[8] They are operator dependent and have demonstrated poor reproducibility in a large multi-centered study of healthy pediatric patients.[34] Thus, it has been postulated that perhaps EF and SF are not the best measures to evaluate cardiac function post-treatment and we worry that cardiac disease may have been underrepresented in our patient cohort.

Alternatively, evaluation of myocardial strain by ECHO may be considered. Myocardial strain is a non-invasive measurement on 2-dimensional speckle tracing ECHO, it is reported as a percentage that can be measured by global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS). Prior studies have demonstrated decreased GLS and GCS despite normal left ventricular EF or SF in childhood cancer survivors, implying the presence of left ventricular systolic dysfunction or subclinical myocardial dysfunction.[35–39] Reduction in GLS by 10%-15% appears to be the most useful parameter for prediction of cardiotoxicity, as it may define a decrease in left ventricular ejection fraction (LVEF) or heart failure. Thus, measures of cardiac strain in late survivors of childhood cancer may be abnormal, even in the context of normal LVEF. The true value in predicting subsequent ventricular dysfunction or heart failure needs to be further evaluated. In a recent article by Martinez et al, the ECHO results from 51 patients treated for pediatric CNS malignancies at Cincinnati Children's Hospital with CSI who had at least one ECHO done after CSI, did not have abnormal left ventricular dysfunction noted.[39] However, the abnormal cardiac strain was demonstrated.[39]

Proton beam RT in brain tumor patients receiving CSI may be advantageous given the lack of "scatter" that is

Table 2. Summary of Cardiac Abnormalities in 5 Medulloblastoma Survivors

Age/ Gender	Risk Diagnosis	Therapies		Years From RT to Abnormal ECHO	Abnormalities		Management of Cardiac Abnormality
		Chemo	CSI dose (Gy)[a]		ECHO (%)	ECG	
13 y, 2 mo/F	AVG	CCG/POG A9961 (CCNU, Cisplatin, Vincristine)	23.4	7.7	EF 31.6	ND	Repeat ECHO24 months later (normal)
8 y, 6 mo/M	AVG	CCG/POG A9961 (CCNU, Cisplatin, Vincristine)	23.4	7.5	EF 34.9	ND	Repeat ECHO 12 months later (normal)
6 y, 7 mo/F	AVG	CCG/POG A9961 (CCNU, Cisplatin, Vincristine)	23.4	5.3	EF 29.6	ND	None
20 y, 4 mo/M	High	POG9631 (Cisplatin, Etoposide, Cyclophosphamide, Vincristine)	39	6.5	SF 27.7	Normal	Cardiac MRI 12 months later (normal), observation
8 y, 6 mo/F	AVG	ACNS0331 (CCNU, Cisplatin, Vincristine, Cyclophosphamide)	23.4	5.7	SF 26.6	Sinus tachy-cardia; border-line prolonged QTc	Repeat ECHO 12 months later (normal)

Abbreviations: AVG, average; CCG, Children's Cancer Group; CSI, craniospinal irradiation; ECG, electrocardiogram; ECHO, echocardiogram; F, female; M, male; m, months; ND, not done; POG, Pediatric Oncology Group; y, years.
[a]All 5 patients also received a 54 Gy boost to the primary tumor.

associated with traditional photon beam RT. As such, protons may eliminate the cardiac RT exposure in patients receiving CSI. Several groups have demonstrated the advantage of proton RT in sparing critical normal structures.[40–46] No late cardiac effects were reported by Yock et al[44] in 59 pediatric medulloblastoma patients treated with proton RT with a median of 7-year follow-up, although no ECGs or ECHOs were performed in their study; therefore, only symptomatic cardiac disease would have been detected. Although proton irradiation "spares" the heart, the hypothalamic-pituitary axis remains affected, which in turn may increase the risk of cardiovascular disease in these survivors.[16] Thus, further studies are needed to determine the presence or absence of asymptomatic cardiac dysfunction in this population.

In our study, variation exists in the management and screening of pediatric cancer survivor patients after completion of therapy.[12,40] It is important to continue to screen for cardiac dysfunction as the pediatric CNS survivorship population reaches older adulthood and acquires more medical morbidity (eg, dyslipidemia and stroke).

While additional studies need to be done to further investigate if cardiac strain should be followed as part of survivorship guidelines in pediatric survivors of CNS tumors, the data by Martinez et al are compelling and should be considered for evaluation of these patients. While additional research is underway, one suggested approach would be to use a multipronged approach to assess for cardiac dysfunction in pediatric CNS survivors based on individual risk, with greater focus on early identification and management of comorbidities, such as decreased exercise tolerance, dyslipidemia, and management of endocrinopathies. In patients that have received CSI, a screening ECG and ECHO should continue to be performed in all patients. In addition to radiation, an assessment of a patient's individual cardiac risk factors, such as ethnicity, obesity, dyslipidemia, inability to perform aerobic exercise due to physical deconditioning or tumor/treatment induced or iron overload should always be factored into any treatment plan.

Our study has limitations. A limited number of repeat ECHOs were performed, which limited our ability to capture changes over time. In addition, radiation doses were limited to spinal or CSI dosing; estimated doses to the cardiac muscle were not available. Furthermore, while our study charts range from 1980 to 2010, the first version of the COG guidelines was only published in 2003, and this is the first time radiation was formally included in cardiotoxicity monitoring recommendations. All patients in our cohort who had ECHOs performed were done following the publication of these recommendations. Prior to this, Steinherz and colleagues published the first imaging recommendations for cardiac monitoring in children in 1992, but this was limited to patients who had received anthracyclines.[41] This may account for the lack of screening in some of the patients in this study, as medulloblastoma patients are not treated with anthracyclines. Although the mean duration from treatment to ECHO monitoring was 7.4 years, most patients underwent only one ECHO evaluation and this could lead to underestimations of long-term cardiac-associated side effects. A large percentage of patients did not have ECHOs completed and were excluded from the study and information is not available. Given that the incidence of cardiac disease increases with age and longer duration of treatment, this relatively young cohort may underestimate the risk of cardiac dysfunction in medulloblastoma survivors. Additional longitudinal studies would be beneficial. Further studies should also evaluate whether access to

care, consistent follow-up, formal survivorship screening programs, or lack of insurance coverage serve as barriers to obtaining imaging. Cardiac health in CNS survivors is multifactorial, as such the weight of each factor is unknown and further studies evaluating other confounding factors such as GH deficiency may be beneficial.

Conclusion

The risk for cardiac morbidity and mortality is multifactorial in childhood CNS tumor survivors, resulting from treatment modalities and their sequelae. Such individuals require ongoing monitoring for these late effects, especially as they approach ages in which cardiovascular and cerebrovascular disease is more prevalent. The risk and extent of cardiac toxicity following CSI is not well documented in the literature, although existent. Long-term, ongoing follow-up in CNS survivors is critical to evaluate the risk of therapy, including late-onset cardiac toxicity. Proton radiation has the potential to deliver spinal radiation while eliminating cardiac dosing and ongoing research will demonstrate if this will help mitigate long-term risk. Further long-term follow-up studies specific to pediatric CNS survivors are needed to better determine cardiac late effects in this population and the frequency and modality of cardiac monitoring, as patients with cardiac abnormalities may be asymptomatic and our current surveillance strategy may not be effective as our patients' transition to adulthood.

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References

1. Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. *J Natl Cancer Inst*. 1999;91(12):1051–1058.
2. Surveillance, Epidemiology, and End Results (SEER) Program. Research Data (1975-2016), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission. www.seer.cancer.gov
3. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2009;101(13):946–958.
4. Robinson KE, Fraley CE, Pearson MM, Kuttesch JF, Compas BE. Neurocognitive late effects of pediatric brain tumors of the posterior fossa: a quantitative review. *J Int Neuropsychol Soc*. 2013;19(1):44–53.
5. Turner CD, Rey-Casserly C, Liptak CC, Chordas C. Late effects of therapy for pediatric brain tumor survivors. *J Child Neurol*. 2009;24(11):1455–1463.
6. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606.
7. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol*. 2013;31(29):3673–3680.
8. Bansal N, Amdani S, Lipshultz ER, Lipshultz SE. Chemotherapy-induced cardiotoxicity in children. *Expert Opin Drug Metab Toxicol*. 2017;13(8):817–832.
9. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. *Nat Rev Cardiol*. 2015;12(9):547–558.
10. Floyd JD, Nguyen DT, Lobins RL, Bashir Q, Doll DC, Perry MC. Cardiotoxicity of cancer therapy. *J Clin Oncol*. 2005;23(30):7685–7696.
11. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2008;100(19):1368–1379.
12. Ryan TD, Border WL, Baker-Smith C, et al. The landscape of cardiovascular care in pediatric cancer patients and survivors: a survey by the ACC Pediatric Cardio-Oncology Work Group. *Cardiooncology*. 2019;5:16.
13. van der Pal HJ, van Dalen EC, Hauptmann M, et al. Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. *Arch Intern Med*. 2010;170(14):1247–1255.
14. Groarke JD, Nguyen PL, Nohria A, Ferrari R, Cheng S, Moslehi J. Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease. *Eur Heart J*. 2014;35(10):612–623.
15. Chojnacka M, Skowrońska-Gardas A, Morawska-Kaczyńska M, Zygmuntowicz-Piętka A, Pędziwiatr K, Semaniak A. Craniospinal radiotherapy in children: electron- or photon-based technique of spinal irradiation. *Rep Pract Oncol Radiother*. 2010;15(1):21–24.
16. Frankart AJ, Nagarajan R, Pater L. The impact of proton therapy on cardiotoxicity following radiation treatment. *J Thromb Thrombolysis*. 2021;51(4):877–883.
17. Madan R, Benson R, Sharma DN, Julka PK, Rath GK. Radiation induced heart disease: pathogenesis, management and review literature. *J Egypt Natl Canc Inst*. 2015;27(4):187–193.
18. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med*. 1991;324(12):808–815.
19. Rao VU, Reeves DJ, Chugh AR, et al. Clinical approach to cardiovascular toxicity of oral antineoplastic agents: JACC state-of-the-art review. *J Am Coll Cardiol*. 2021;77(21):2693–2716.
20. Babiker HM, McBride A, Newton M, et al. Cardiotoxic effects of chemotherapy: a review of both cytotoxic and molecular targeted oncology therapies and their effect on the cardiovascular system. *Crit Rev Oncol Hematol*. 2018;126:186–200.
21. de Ville de Goyet M, Moniotte S, Robert A, et al. Iron overload in children undergoing cancer treatments. *Pediatr Blood Cancer*. 2013;60(12):1982–1987.

22. Emy PY, Levin TL, Sheth SS, Ruzal-Shapiro C, Garvin J, Berdon WE. Iron overload in reticuloendothelial systems of pediatric oncology patients who have undergone transfusions: MR observations. *AJR Am J Roentgenol*. 1997;168(4):1011–1015.
23. Ruccione KS, Wood JC, Sposto R, Malvar J, Chen C, Freyer DR. Characterization of transfusion-derived iron deposition in childhood cancer survivors. *Cancer Epidemiol Biomarkers Prev*. 2014;23(9):1913–1919.
24. Schempp A, Lee J, Kearney S, Mulrooney DA, Smith AR. Iron overload in survivors of childhood cancer. *J Pediatr Hematol Oncol*. 2016;38(1):27–31.
25. Sait S, Zaghloul N, Patel A, Shah T, Iacobas I, Calderwood S. Transfusion related iron overload in pediatric oncology patients treated at a tertiary care centre and treatment with chelation therapy. *Pediatr Blood Cancer*. 2014;61(12):2319–2320.
26. Darzy KH, Shalet SM. Hypopituitarism following radiotherapy revisited. *Endocr Dev*. 2009;15:1–24.
27. Merchant TE, Rose SR, Bosley C, Wu S, Xiong X, Lustig RH. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Clin Oncol*. 2011;29(36):4776–4780.
28. Rutter MM, Rose SR. Long-term endocrine sequelae of childhood cancer. *Curr Opin Pediatr*. 2007;19(4):480–487.
29. Mulder RL, Kremer LC, van Santen HM, et al. Prevalence and risk factors of radiation-induced growth hormone deficiency in childhood cancer survivors: a systematic review. *Cancer Treat Rev*. 2009;35(7):616–632.
30. Cooksey R, Wu SY, Klesse L, et al. Metabolic syndrome is a sequela of radiation exposure in hypothalamic obesity among survivors of childhood brain tumors. *J Investig Med*. 2019;67(2):295–302.
31. Pietilä S, Mäkipernaa A, Sievänen H, Koivisto AM, Wigren T, Lenko HL. Obesity and metabolic changes are common in young childhood brain tumor survivors. *Pediatr Blood Cancer*. 2009;52(7):853–859.
32. Talvensaari KK, Lanning M, Tapanainen P, Knip M. Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. *J Clin Endocrinol Metab*. 1996;81(8):3051–3055.
33. Pellikka PA, She L, Holly TA, et al. Variability in ejection fraction measured by echocardiography, gated single-photon emission computed tomography, and cardiac magnetic resonance in patients with coronary artery disease and left ventricular dysfunction. *JAMA Netw Open*. 2018;1(4):e181456.
34. Frommelt PC, Minich LL, Trachtenberg FL, et al. Challenges with left ventricular functional parameters: the pediatric heart network normal echocardiogram database. *J Am Soc Echocardiogr*. 2019;32(10):1331–1338.e1.
35. Akam-Venkata J, Kadiu G, Galas J, Lipshultz SE, Aggarwal S. Left ventricle segmental function in childhood cancer survivors using speckle-tracking echocardiography. *Cardiol Young*. 2019;29(12):1494–1500.
36. Pignatelli RH, Ghazi P, Reddy SC, et al. Abnormal myocardial strain indices in children receiving anthracycline chemotherapy. *Pediatr Cardiol*. 2015;36(8):1610–1616.
37. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014;63(25 Pt A):2751–2768.
38. Yu AF, Raikhelkar J, Zabor EC, et al. Two-dimensional speckle tracking echocardiography detects subclinical left ventricular systolic dysfunction among adult survivors of childhood, adolescent, and young adult cancer. *Biomed Res Int*. 2016;2016:9363951.
39. Martinez HR, Salloum R, Wright E, et al. Echocardiographic myocardial strain analysis describes subclinical cardiac dysfunction after craniospinal irradiation in pediatric and young adult patients with central nervous system tumors. *Cardiooncology*. 2021;7(1):5.
40. Bhatia N, Lenihan D, Sawyer DB, Lenneman CG. Getting the SCOOP-survey of cardiovascular outcomes from oncology patients during survivorship. *Am J Med Sci*. 2016;351(6):570–575.
41. Steinherz LJ, Graham T, Hurwitz R, et al. Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the Cardiology Committee of the Childrens Cancer Study Group. *Pediatrics*. 1992;89(5 Pt 1):942–949.
42. St Clair WH, Adams JA, Bues M, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2004;58(3):727–734.
43. Al-Wassia RK, Ghassal NM, Naga A, Awad NA, Bahadur YA, Constantinescu C. Optimization of craniospinal irradiation for pediatric medulloblastoma using VMAT and IMRT. *J Pediatr Hematol Oncol*. 2015;37(7):e405–e411.
44. Yock TI, Yeap BY, Ebb DH, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. *Lancet Oncol*. 2016;17(3):287–298.
45. Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2013;86(2):277–284.
46. Yuh GE, Loredo LN, Yonemoto LT, et al. Reducing toxicity from craniospinal irradiation: using proton beams to treat medulloblastoma in young children. *Cancer J*. 2004;10(6):386–390.