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Meta-analysis of the incidence and patterns of second neoplasms after photon craniospinal irradiation in children with medulloblastoma

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Abstract

Background: Second neoplasms (SNs) are a well-established long-term adverse effect of radiation therapy (RT), but there are limited data regarding their incidence and location relative to the radiation field, specific to medulloblastoma (MB) survivors after craniospinal irradiation (CSI).

Methods: A systematic literature review, per Preferred Reporting Items for Systematic Reviews and Meta-Analyses, identified six studies reporting the incidence and locations of SNs for 1,114 patients with MB, after CSI, with a median follow-up of ~9 years (7.6–15.4 years). The study-specific cumulative incidence (CI) of SNs, second benign neoplasms (SBNs), and second malignant neoplasms (SMNs) were standardized to a 10-year time frame. Meta-analysis was performed using random effects models, with pooled data from selected studies and an institutional cohort of 55 patients.

Results: The 10-year CI was 6.1% for all SNs (excluding skin cancer and leukemia), 3.1% for SBNs, and 3.7% for SMNs. Fifty-eight percent of SNs were malignant; high-grade glioma was the most common SMN (15/33; 45%) and meningioma, the most common SBN (16/24; 67%). Forty percent of SNs occurred outside the target central nervous system (CNS) field, with a majority in areas of exit RT dose. Seventy-four percent of extra-CNS tumors (17/23) were malignant, most commonly thyroid carcinoma (7/17; 41%) and bone and soft-tissue tumors (6/17, 35%).

Conclusions: Survivors of MB are at risk of SNs both within and outside the CNS. A significant proportion of SNs occur in areas of exit RT dose. Studies are needed to determine whether the use of proton therapy, which has no exit RT dose, is associated with a lower incidence of SNs.

KEYWORDS
craniospinal irradiation, medulloblastoma, photon radiation, second neoplasms

1 | INTRODUCTION

Survival has improved significantly for patients with medulloblastoma (MB), with craniospinal irradiation (CSI) and chemotherapy,[1,2] but at the cost of long-term adverse effects including second neoplasms (SNs).[3] SNs are a known long-term adverse effect of radiation therapy (RT),[4,5] with the risk increasing with RT dose and follow-up.[6,7] Second malignant neoplasms (SMNs) are the most common cause of death in childhood central nervous system (CNS) tumor survivors more than 10 years off-therapy,[8] with the most common SMNs after RT being solid tumors, both within the target radiation field (gliomas and meningiomas) and outside the target field (thyroid cancer and sarcomas).[9]

Reports by the Childhood Cancer Survivor Study (CCSS), British cancer registry, from SEER data, as well as single institutions, describe the incidence and characteristics of SNs for patients with CNS tumors as a group. However, the volumes and doses of RT for these patients differ significantly based on their diagnosis. There are limited data on the incidence of SNs and their locations relative to the RT field, specific to MB, for which the volume irradiated is significantly greater compared to most other CNS tumors which are treated with

Abbreviations: BCM, Baylor College of Medicine; CNS, central nervous system; CSI, craniospinal irradiation; MB, medulloblastoma; RT, radiation therapy; SMNs, second malignant neoplasms; TCH, Texas Children's Hospital

focal/involved-field RT (e.g. gliomas and ependymoma). Consequently, in patients with MB, a significantly larger volume of healthy tissue receives an exit RT dose, with the associated risk of SNs.

We performed a meta-analysis of the incidence and locations of SNs, relative to the radiation field, for patients treated for MB, with radiation to the craniospinal axis. The analysis included previously unpublished data from a single institution and the existing literature identified by a systematic review.

2 | METHODS

2.1 | Systematic literature search

A systematic search of the literature was conducted, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method. A search strategy was developed for Medline (Ovid) using the following Medical Subject Heading terms: medulloblastoma; nervous system neoplasms; brain neoplasms; radiotherapy; radiotherapy, adjuvant; neoplasms, second primary; neoplasms, radiation-induced; child; pediatrics; and adolescent. Appropriate synonyms were determined and searched for as text in article titles, abstracts, and keywords. This search strategy, listed in full in Supplementary Document S1, was then translated to the Embase, Scopus, and PubMed databases. After internal and external deduplication, 2,076 unique titles from the literature search were identified.

2.2 | Eligibility criteria and data extraction

In order for studies to be eligible for this meta-analysis, they needed to report data regarding the incidence and nature of SNs for a cohort of at least five patients with MB treated with CSI, with a median follow-up of at least 5 years. The studies could be prospective or retrospective. Two authors (A.B. and S.T.) independently reviewed all 2,076 titles and identified relevant studies (Figure 1). In case of a disagreement, the two reviewers were to first attempt to reach a consensus by discussion, failing which, they were to proceed to arbitration by the senior author (A.C.P.). All titles were initially screened by review of title and abstract, to determine eligibility. Selected publications that appeared to be on topic were then assessed in detail to ascertain data availability, completeness, and relevance based on the predetermined inclusion criteria. Papers with missing or duplicated data were further excluded. For eligible studies, data were extracted as available, including the number of patients with MB treated with CSI, patient characteristics and demographics, details of surgery and chemotherapy, dose of CSI, radiation technique, median follow-up, cumulative incidence (CI) of SNs, second benign neoplasms (SBNs) and SMNs, median interval between RT and occurrence of SNs, and the number and characteristics of SNs in the target field and outside the target field.

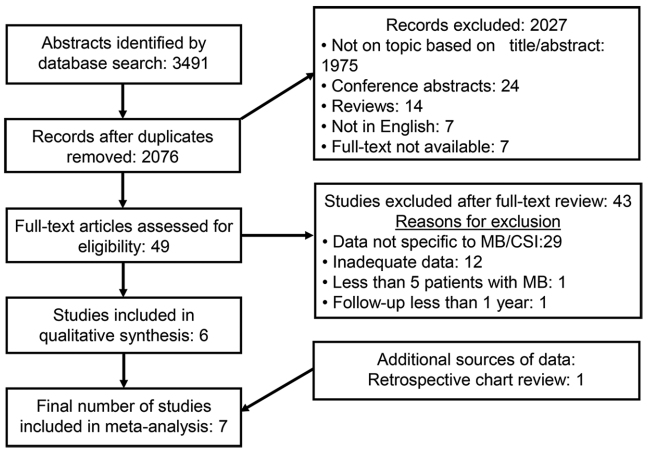

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

2.3 | Retrospective study at a single institution

Data were included, in this meta-analysis, from a retrospective study of a cohort of 55 consecutive patients with MB, treated at a single institution—Texas Children's Hospital (TCH)/Baylor College of Medicine (BCM)—between January 1997 and October 2008. Approval was obtained for this study from the institutional review board at TCH/BCM.

2.4 | Statistical analysis

Ten-year CI rates were determined for the following: (a) all SNs (excluding skin cancer and leukemia), (b) SBNs, (c) SMNs, and (d) skin cancer. This process involved obtaining the median time to follow-up for all patients either directly from the manuscript, or by obtaining the overall survival at 3, 5, or 10 years and interpolating to get the median time to follow-up for all subjects from the median time to follow-up for surviving subjects. The study-specific incidence rates were then standardized to a 10-year time frame. Random effects models were used in the meta-analysis and the combined 10-year CI of SNs was estimated and tabulated along with 95% confidence intervals.

Forest plots illustrating this information were constructed. This was done for all, benign, malignant, and skin SNs, within and outside the CNS, that is, the target radiation field. Meta-analyses were performed using MedCalc for Windows, version 18.0 (MedCalc Software, Ostend, Belgium). The random effects weighting was implemented using the Freeman–Tukey transformation.

3 | RESULTS

3.1 | Systematic literature review

Data from the single-institution (TCH) retrospective review were pooled with that from six papers identified, by systematic review of the literature, as meeting inclusion criteria for the meta-analysis (Table 1).[3,10–14] The systematic search of databases yielded 2,076 titles, of which, 1,975 titles were excluded as "not on topic" by review of the title and/or abstract (Figure 1). Further excluded were 24 conference abstracts, 14 reviews, seven manuscripts in a language other than English, and seven abstracts for which full manuscripts could not

TABLE 1 Characteristics of included studies

Study	PMID	Study population	Era	Craniospinal RT dose (Gy) median/range	Sample size	Median f/u (years)
Packer et al.	23099653	COG A9961[a]	1996–2000	23.4	379	8.9
Christopherson et al.[10]	24564687	University of Florida	1963–2008	28.8	53	15.4
Stavrou et al.[11]	11878577	CNMC	1969–1997	32–36	82	7.6
Helseth et al.[12]	10502004	NH and NRH	1973–1997	30–36	28	13.5
von Hoff et al.[13]	19250820	HIT'91[a]	1991–1997	35.2	280	8.8
Tsui et al.[14]	25395462	SJCRH	1985–2012	NR	237	10.3
Bavle et al.	N/A	TCH	1997–2008	26	55	8.1

[a]Prospective treatment trial for medulloblastoma.

PMID, Pubmed ID; RT, radiation therapy; f/u, follow-up; COG, Children's Oncology Group; CNMC, Children's National Medical Center, Washington DC; NH and NRH, The National Hospital and National Radium Hospital in Norway; HIT'91, prospective treatment trial for medulloblastoma; SJCRH, St. Jude Children's Research Hospital; TCH, Texas Children's Hospital; N/A, not applicable; NR, not reported.

be obtained. The remaining 49 manuscripts were reviewed in detail, with 43 of these papers being excluded despite describing SNs after RT due to a lack of data specific to MB/primitive neuroectodermal tumor or CSI in 29 papers; results specific to MB, but with inadequate data for meta-analysis in 12 studies[7,15–25] (Supplementary Table S1); and less than five patients with MB[26] and median follow-up less than 1 year[27] in one study each. Both reviewers (A.B. and S.T.) agreed that the identified studies met inclusion criteria.

3.2 | CI of SNs

For 1,114 patients with MB treated with CSI, the overall CI of SNs (excluding skin cancer), benign and malignant, within and outside the CNS (i.e. the target radiation field), are reported in Table 2, Figure 2, and Supplementary Document S2. Fifty-eight percent (33/57) of SNs were malignant (Table 3) and high-grade glioma was the most common SMN (15/33; 45%). Meningioma was the most common SBN (16/24; 67%). Two patients had low-grade gliomas and one an anaplastic meningioma, with a total of 34 patients developing second tumors in the CNS.

Forty percent of SNs (23/57) occurred outside the CNS (Table 3). The most common extra-CNS location for SNs was the thyroid gland (10/23; 43%). Seventy-four percent of extra-CNS tumors (17/23) were malignant, most commonly thyroid carcinoma (7/17; 41%). Nearly two-thirds of extra-CNS SNs (15/23; 65%) were in areas known to receive exit radiation, while some bone and soft tissue tumors (5/23; 22%) occurred in the skull, jaw, and nasal cavity, all structures exposed to entry radiation. The location of SN was not specified for three patients with osteosarcoma and nerve sheath and desmoid tumors, respectively (Table 3).

The 10-year CI of skin malignancies was 1.1 %, with all but one patient reported to have basal cell carcinoma (7/8; 88%). Nearly half these patients (3/8; 38%) had a diagnosed germline predisposition syndrome (Gorlin or nevoid basal cell carcinoma syndrome).

TABLE 2 Ten-year cumulative incidence of second neoplasms

Site of SN	SBNs (%) (95% CI)	SMNs (%) (95% CI)	SNs (%) (95% CI)
Within CNS	2.1 (0.9–3.7)	1.9 (1.2–2.8)	3.5 (2.1–5.3)
Outside CNS	0.8 (0.1–2.2)	2.0 (1.1–3.1)	2.7 (1.3–4.5)
Overall	3.1 (1.4–5.3)	3.7 (2.7–4.9)	6.1 (4.1–8.4)

SN, second neoplasm; SBNs, second benign neoplasms; SMNs, second malignant neoplasms; CNS, central nervous system.

4 | DISCUSSION

The results of this meta-analysis highlight the increased risk of SNs for patients with MB compared to other primary CNS tumors; the 10-year CI of 6.1% for SNs and 3.7% for SMNs is significantly higher for patients with MB compared to those reported for all CNS tumors as a group (1.9% and 1.4–1.7%, respectively).[16,20] This is likely due to the larger volume of radiation (craniospinal) received by patients with MB compared to other CNS tumors which are treated with involved-field radiation (e.g. ependymoma and gliomas).

The 10-year CI in this study is also high compared to results from larger population-based studies that could not be included for meta-analysis (see reasons for exclusion in Supplementary Table S1), with a reported CI of 3% and 4.4% at 10 years in the SEER[16] and St. Jude Children's Research Hospital[20] databases, respectively, and 7.8% at 30 years in the CCSS cohort.[19] This discrepancy could be due to an underestimation of SN incidence in the larger studies caused by loss to follow-up, or an overestimation of SNs in our meta-analysis caused by the inclusion of smaller institutional studies. Consistent with our study, analysis of the SEER database found brain tumors to be the most common SMN after treatment for MB, followed by thyroid cancer.[17]

We identified six studies in the literature that reported the incidence of SNs for cohorts of patients with MB treated with craniospinal

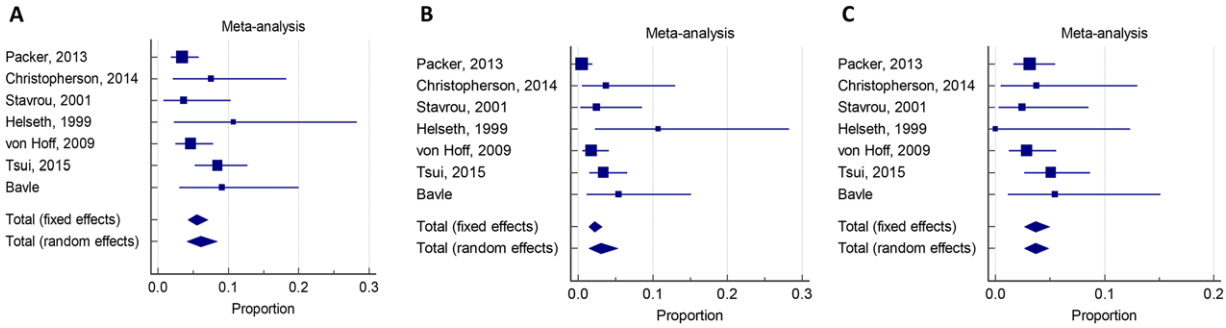

FIGURE 2 Forest plots of pooled analysis with random effects depict the cumulative incidence with 95% confidence interval for (A) second neoplasms, (B) second benign neoplasms, and (C) second malignant neoplasms

radiation. As individual studies, these reports have limited numbers of patients with MB, and hence provide a less robust picture of the CI and patterns of location of SNs relative to the radiation field in this specific patient population. A meta-analysis with pooled data from these studies helps address this challenge, estimating the CI for a total of 1,114 patients with a median follow-up of ~9 years (7.6–15.4 years). The results highlight the significant toxicities of radiation—a crucial treatment modality for disease cure. While more than a third of these tumors were benign, and hence likely curable, their treatment would often involve surgery (e.g. meningioma and thyroid papilloma) and the resulting morbidity. More than half of the reported SNs were malignant, with many of these tumors considered incurable (e.g. glioblastoma multiforme) or with poor survival (e.g. osteosarcoma).

More than a third of SNs occurred outside the intended target radiation field. While some occurred in areas that would receive entry radiation, at least 65% percent of these cases involved areas predicted to receive exit radiation. A promising strategy to reduce the incidence of SNs is to minimize exit radiation with the use of protons, particles that emit most of their energy within a few millimeters of a particular depth (Bragg peak) which can be aligned with the target tumor depth.[28] Brodin et al. reported fewer life years lost for patients with MB treated with intensity-modulated proton therapy compared to two photon radiation techniques (3D conformal radiotherapy and volumetric modulated arc therapy), based on excess hazard ratios for second cancers and cardiac complications in the exit dose region.[29] However, this study did not take into account SMNs within the CNS, which constituted nearly half of the cases in our analysis. This significant adverse event must be considered in future modeling studies estimating the risk of late effects of CSI. One retrospective study largely with adult patients[30] and another using a prediction model[31] also suggest a reduced risk of SMNs with protons compared to conventional photon RT. Prospective studies with proton RT in a pediatric MB cohort, with sufficiently long follow-up, are needed to determine the effectiveness of this strategy.

TABLE 3 Characteristics of second neoplasms

Second neoplasm location (total)	Second benign neoplasms	Second malignant neoplasms
Overall (57)	24 (42%)	33 (58%)
Within CNS (34)	18 (53%)	16 (47%)
Outside CNS (23)	6 (26%)	17 (74%)
	- Thyroid adenoma (3) - Osteoma of jaw (1) - Desmoid tumor[a] (1) - Cardiac tumor (1)[b]	- Thyroid carcinoma (7) - Osteosarcoma[c] (3) - Soft-tissue tumors (3)[d] - Testicular mixed malignant germ cell tumor (1) - Ovarian adenocarcinoma (1) - Salivary gland carcinoma (1)[e] - Intestinal adenocarcinoma (1)

[a]Desmoid tumor location not specified.
[b]Not biopsied and counted as benign tumor for analysis.
[c]Osteosarcoma of skull and temporal bone, with location not specified for one patient.
[d]Soft-tissue tumors included nasal cavity rhabdomyosarcoma, nasal spindle cell carcinoma, and nerve sheath tumor, location not specified.
[e]Mammary analog secretory carcinoma.
CNS, central nervous system.

Only two of six studies in this meta-analysis were prospective with all patients receiving uniform treatment.[3,13] The remaining four studies and the outcomes of the TCH cohort were retrospective reports from single institutions. Study populations were treated in different treatment eras, ranging from 1963 to 2012. The type and intensity of chemotherapy and the dose and modality of radiation delivery have evolved significantly over this time period. The exit dose of radiation is likely to have been greater with older modalities of conventional radiation, while being better limited with more modern techniques such as intensity-modulated RT (IMRT). Indeed, of seven studies, five reported outcomes for patients treated prior to the late 1990s, when IMRT began to be more widely used. The risk of SNs has been unequivocally demonstrated previously to correlate with radiation dose. The dose of radiation in this meta-analysis varied (23.4–36 Gy), with the median RT dose being less than 30 Gy in three studies, greater than 30 Gy in three studies, and not being reported in one study. The available data were inadequate to analyze the impact of this factor on the incidence of SNs. Due to the unavailability of data regarding the actual radiation fields received by patients, solid tumors occurring outside the CNS were presumed to occur due to entry or exit radiation in our analysis. Other factors, such as chemotherapy and undiagnosed germline cancer predisposition syndromes, could have contributed to the occurrence

of some of these SNs, and could not be evaluated in our study. The follow-up in studies was not long enough to determine the incidence and nature of SNs in subsequent decades beyond 10 years, an important consideration in long-term survivors of pediatric tumors. Studies of late effects of treatment for pediatric CNS tumors have shown a continued increased incidence of SNs such as meningiomas and thyroid cancer with longer follow-up.[17,19] The morbidity and mortality of SNs for patients could also not be determined in this analysis.

This meta-analysis strengthens the conclusion of smaller studies, that patients with MB treated with CSI are at risk for a variety of SNs with a wide anatomic distribution, reflective of the large radiation volume. A significant proportion of these SNs occur outside the target radiation field, highlighting the importance of minimizing exit radiation.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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REFERENCES

1. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol*. 2006;7:813–820.
2. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol*. 2006;24:4202–4208.
3. Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. *Neuro Oncol*. 2013;15:97–103.
4. Meadows AT, Baum E, Fossati-Bellani F, et al. Second malignant neoplasms in children: an update from the Late Effects Study Group. *J Clin Oncol*. 1985;3:532–538.
5. Kingston JE, Hawkins MM, Draper GJ, Marsden HB, Kinnier Wilson LM. Patterns of multiple primary tumours in patients treated for cancer during childhood. *Br J Cancer*. 1987;56:331–338.
6. Garwicz S, Anderson H, Olsen JH, et al. The Nordic Society for Pediatric Hematology and Oncology, The Association of the Nordic Cancer Registries. Second malignant neoplasms after cancer in childhood and adolescence: a population-based case-control study in the 5 Nordic countries. *Int J Cancer*. 2000;88:672–678.
7. 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;101:946–958.
8. Morris EB, Gajjar A, Okuma JO, et al. Survival and late mortality in long-term survivors of pediatric CNS tumors. *J Clin Oncol*. 2007;25:1532–1538.
9. Armstrong GT. Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. *Eur J Paediatr Neurol*. 2010;14:298–303.
10. Christopherson KM, Rotondo RL, Bradley JA, et al. Late toxicity following craniospinal radiation for early-stage medulloblastoma. *Acta Oncol*. 2014;53:471–480.
11. Stavrou T, Bromley CM, Nicholson HS, et al. Prognostic factors and secondary malignancies in childhood medulloblastoma. *J Pediatr Hematol Oncol*. 2001;23:431–436.
12. Helseth E, Due-Tonnessen B, Wesenberg F, Lote K, Lundar T. Posterior fossa medulloblastoma in children and young adults (0–19 years): survival and performance. *Childs Nerv Syst*. 1999;15:451–455.
13. von Hoff K, Hinkes B, Gerber NU, et al. Long-term outcome and clinical prognostic factors in children with medulloblastoma treated in the prospective randomised multicentre trial HIT'91. *Eur J Cancer*. 2009;45:1209–1217.
14. Tsui K, Gajjar A, Li C, et al. Subsequent neoplasms in survivors of childhood central nervous system tumors: risk after modern multimodal therapy. *Neuro Oncol*. 2015;17:448–456.
15. Peterson KM, Shao C, McCarter R, MacDonald TJ, Byrne J. An analysis of SEER data of increasing risk of secondary malignant neoplasms among long-term survivors of childhood brain tumors. *Pediatr Blood Cancer*. 2006;47:83–88.
16. Devarahally SR, Severson RK, Chuba P, Thomas R, Bhambhani K, Hamre MR. Second malignant neoplasms after primary central nervous system malignancies of childhood and adolescence. *Pediatr Hematol Oncol*. 2003;20:617–625.
17. Ning MS, Perkins SM, Dewees T, Shinohara ET. Evidence of high mortality in long term survivors of childhood medulloblastoma. *J Neurooncol*. 2015;122:321–327.
18. Goldstein AM, Yuen J, Tucker MA. Second cancers after medulloblastoma: population-based results from the United States and Sweden. *Cancer Causes Control*. 1997;8:865–871.
19. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2010;102:1083–1095.
20. Broniscer A, Ke W, Fuller CE, Wu J, Gajjar A, Kun LE. Second neoplasms in pediatric patients with primary central nervous system tumors: the St. Jude Children's Research Hospital experience. *Cancer*. 2004;100:2246–2252.
21. Hawkins MM, Draper GJ, Kingston JE. Incidence of second primary tumours among childhood cancer survivors. *Br J Cancer*. 1987;56:339–347.
22. Berger C, Trombert-Paviot B, Casagranda L, et al. Second malignant neoplasms following childhood cancer: a study of a recent cohort (1987–2004) from the childhood cancer registry of the Rhone-Alpes region (ARCERRA) in France. *Pediatr Hematol Oncol*. 2011;28:364–379.
23. Haddy TB, Mosher RB, Dinndorf PA, Reaman GH. Second neoplasms in survivors of childhood and adolescent cancer are often treatable. *J Adolesc Health*. 2004;34:324–329.
24. Casey DL, Friedman DN, Moskowitz CS, et al. Second cancer risk in childhood cancer survivors treated with intensity-modulated radiation therapy (IMRT). *Pediatr Blood Cancer*. 2015;62:311–316.
25. Caglar K, Varan A, Akyuz C, et al. Second neoplasms in pediatric patients treated for cancer: a center's 30-year experience. *J Pediatr Hematol Oncol*. 2006;28:374–378.
26. Salgado D, Nunes S, Pereira P, Vinhais S. Oh, no…not again! Second intracranial tumors in pediatric brain tumor survivors. *Neuro Oncol*. 2014;16:i111–i116.

27. Ince D, Mutafoglu K, Kizmazoglu D, et al. A single center experience of a treatment for medulloblastoma. *Pediatr Blood Cancer*. 2016;63:S134.
28. Gondi V, Yock TI, Mehta MP. Proton therapy for paediatric CNS tumours—improving treatment-related outcomes. *Nat Rev Neurol*. 2016;12:334–345.
29. Brodin NP, Vogelius IR, Maraldo MV, et al. Life years lost—comparing potentially fatal late complications after radiotherapy for pediatric medulloblastoma on a common scale. *Cancer*. 2012;118:5432–5440.
30. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. *Int J Radiat Oncol Biol Phys*. 2013;87:46–52.
31. Moteabbed M, Yock TI, Paganetti H. The risk of radiation-induced second cancers in the high to medium dose region: a comparison between passive and scanned proton therapy, IMRT and VMAT for pediatric patients with brain tumors. *Phys Med Biol*. 2014;59:2883–2899.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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