Original Article

Overall Survival and Secondary Malignant Neoplasms in Children Receiving Passively Scattered Proton or Photon Craniospinal Irradiation for Medulloblastoma

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BACKGROUND: Both intensity-modulated radiotherapy (RT) and passively scattered proton therapy have a risk of secondary malignant neoplasm (SMN) in children. To determine the influence of RT modality on the incidence of SMN after craniospinal irradiation (CSI), the authors compared the incidence of SMN in children who had medulloblastoma treated with either photon CSI plus an intensity-modulated RT boost (group I) or passively scattered proton CSI plus a boost (group II). **METHODS:** From 1996 to 2014, 115 children with medulloblastoma (group I, n = 63; group II, n = 52) received CSI followed by a boost to the tumor bed. Most patients had standard-risk disease (63.5%). The median follow-up was 12.8 years for group I and 8.7 years for group II. **RESULTS:** The 5-year and 10-year overall survival (OS) rates were 88.8% and 85.1%, respectively, for standard-risk patients and 63.1% and 57.3%, respectively, for high-risk patients, with no OS difference by RT modality (P = .81). Six SMNs were identified (4 in group I, 2 in group II). The 5-year and 10-year SMN incidence rates were 1.0% and 6.9%, respectively (0.0% and 8.0%, respectively, in group I; 2.2% and 4.9%, respectively, in group II; P = .74). Two SMNs occurred in the clinical target volume in the brain, 2 occurred in the exit dose region from the photon spinal field, 1 occurred in the entrance path of a proton beam, and 1 occurred outside the radiation field. There were no reported cases of secondary leukemia. **CONCLUSIONS:** This analysis demonstrates no difference in OS or SMN incidence between patients in groups I and II 10 years after RT. ***Cancer* 2021;127:3865-3871**. © *2021 American Cancer Society*.

LAY SUMMARY:

- One hundred fifteen children with medulloblastoma received radiotherapy (RT) with either photon craniospinal irradiation (CSI) and an intensity-modulated RT boost (group I; n = 63) or passively scattered proton CSI and a boost (group II;, n = 52).
- The majority of children had standard-risk disease (63.5%).
- The 5-year and 10-year overall survival rates were 88.8% and 85.1% for standard-risk patients, respectively, and 63.1% and 57.3% for high-risk patients, respectively, with no difference in overall survival by RT group (P = .81).
- The 5-year and 10-year second malignant neoplasm incidence rates were 1.0% and 6.9%, respectively, with no difference in second malignant neoplasm incidence according to RT group (P = .74).

KEYWORDS: intensity-modulated radiation therapy, medulloblastoma, proton, radiotherapy, secondary malignant neoplasm.

INTRODUCTION

Although survival outcomes in children with medulloblastoma have improved with surgery, radiotherapy (RT), and chemotherapy (CT), treatment-related late effects continue to be problematic. In a recent report from the Childhood Cancer Survivor Study, survivors treated with multimodality therapy (surgery, RT, and CT) had more hearing loss, cardiovascular problems (including stroke), and secondary neoplasms compared with historic therapy (surgery and RT).[1] Recent strategies in pediatric oncology have included the use of more conformal RT as well as proton therapy (PT) to minimize late effects. Craniospinal irradiation (CSI) using PT reduces the dose to the heart, lungs, abdominal organs, and pelvic organs, which may translate to a more favorable cardiovascular, pulmonary, gastrointestinal, and reproductive toxicity profile. Likewise, based on several modeling studies, the lack of an exit dose from the spinal field with PT may reduce the predicted risk of a secondary cancer in various organs.[2,3] However, the theoretical lower risk of developing a secondary malignant neoplasm (SMN) with PT may only be seen with spot scanning and not with passively scattered PT because of an increased total body dose secondary to neutrons.[4,5] Similarly,

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intensity-modulated RT (IMRT) has the potential to increase the incidence of SMN because of more monitor units, leakage radiation, and a larger volume of normal tissue exposed to low-dose radiation.[5] With the above potential benefits and theoretical risks of SMN with both passively scattered PT and IMRT, we reviewed the records of patients with medulloblastoma who received CSI over a span of almost 2 decades.

MATERIALS AND METHODS

After approval from the Institutional Review Board, we conducted a retrospective review of the records of patients aged <18 years who had medulloblastoma diagnosed at Texas Children's Hospital from 1996 to 2014. Before 2006, all patients were treated with photon therapy; thereafter, all patients received PT. For photon therapy (group I), CSI was delivered using 3-dimensional RT (3DRT) with 2 opposed lateral fields for the brain and upper cervical spinal region abutted to 1 or 2 posterior-anterior spinal fields. CSI was followed by an IMRT boost(s) to the posterior fossa and/or the tumor bed, depending on the treatment protocol. Patients treated with PT (group II) received passively scattered PT with right and left posterior oblique fields abutted to posterior-anterior fields. This was followed by a tumor bed PT boost. The techniques of CSI treatment delivery with photon RT and PT for our patients have been described previously.[6-8] In general, patients with standard-risk disease received from 18.0 to 23.4 gray (Gy) of CSI followed by either a boost to the entire posterior fossa and tumor bed (St Jude Medulloblastoma study 96 [SJMB96]) or a boost to the tumor bed alone. Patients with high-risk disease received from 36.0 to 39.6 Gy of CSI followed by either a posterior fossa boost (SJMB96) or a boost to the tumor bed alone. In some patients with standard-risk disease, CSI doses were either 30.6 Gy or 36.0 Gy because of concerns of more aggressive histology (large cell, anaplastic). In 1 patient with high-risk disease, 34.2-Gy CSI using photons was delivered because of the acute toxicity of treatment. None of the patients received cone-beam computed tomography for daily treatment verification. The CT delivered was primarily based on St Jude or Children's Oncology Group (COG) protocol guidelines.

SMNs were discovered by routine imaging during tumor surveillance or in the long-term follow-up clinic by examination or patient symptomatology, which led to further workup. Pathologic confirmation of the SMN was performed with the exception of 1 patients in whom there was parental refusal for a biopsy. For a tumor to be classified as an SMN, it had to be a tumor that was not a medulloblastoma.

The χ^2 test was used to compare the proportion of patients receiving photon therapy (group I) or PT (group II) according to host, tumor, and treatment characteristics. The Fisher exact test was used to compare the proportion of patients developing an SMN according to host, tumor, and treatment characteristics. The overall survival (OS) rates and the cumulative incidence function of SMN were estimated using the Kaplan-Meier method. Patients were censored at the last follow-up date if they had not developed an SMN. Differences in OS rates and SMN incidence were examined using the log-rank test. SPSS statistical software was used for the analysis, in which $P < .05$ was considered statistically significant.

RESULTS

There were 115 children with medulloblastoma seen and treated with CSI during the time period. There were 80 male (69.6%) and 35 female (30.4%) patients. The median patient age was 7 years (range, 3-17 years) at the time of RT. Seventy-three patients had standard-risk disease (63.5%). RT was delivered with photon RT in 63 patients (54.8%; group I) or with PT in 52 patients (45.2%; group II). The CSI dose was from 18.0 to 23.4 Gy in 70 patients (60.9%) and from 30.6 to 39.6 Gy (39.1%) in 45 patients. Dose to the tumor bed was either 54.0 or 55.8 Gy. The most common CT regimens were based on SJMB03 (n = 49), SJMB96 (n = 28), COG A9961 (n = 24), COG ACNS 0334 (n = 5), COG ACNS 0331 (n = 4), and other (n = 5). The distribution of patient, tumor, and treatment characteristics according to RT modality (group I vs group II) is provided in Table 1. There was no difference in the distribution of patients according to sex, age at RT (≤7 or >7 years), risk category, CSI dose (18.0-23.4 vs 30.6-39.6 Gy), or type of CT (SJMB vs COG and other). The median patient age at time of RT was 7.1 years for group I and 7.0 years for group II. None of the patients had a known tumor predisposition syndrome such as Li-Fraumeni syndrome or Gorlin syndrome. All patients who were treated using the SJMB96 protocol received photon therapy, whereas 38 of 49 patients (77.6%) who were treated using the SJMB03 protocol received PT. For COG A9961, 21 patients received photons and 3 received protons; whereas, for COG ACNS0331 and ACNS0334, all patients received protons. The median follow-up after completion of RT was 12.8 years (range,

TABLE 1. Distribution of Patient, Tumor, and Treatment Parameters of Children According to Radiation Modality

Parameter	No. of Patients		P^a
	Group I: Photon RT, n = 63	Group II: Proton RT, n = 52	
Sex			.89
Male	43	37	
Female	20	15	
Age at RT, y			.92
≤7	31	27	
>7	32	25	
Risk category			1.00
Standard	40	33	
High	23	19	
CSI dose, Gy			.95
18.0-23.4	39	31	
30.6-40.0	24	21	
Chemotherapy			.29
SJMB96/ SJMB03	39	38	
COG/other	24	14	

Abbreviations: COG, Children's Oncology Group; CSI, craniospinal irradiation; Gy, gray; RT, radiotherapy; SJMB96/SJMB03, St Jude medulloblastoma studies 96 and 03, respectively.
[a]*P* values were determined using the χ^2 test.

0.2-20.3 years) for group I and 8.7 years (range, 0.4-13.4 years) for group II.

Overall Survival

The 5-year and 10-year OS rates were 79.4% and 75.1%, respectively, for all patients. The 5-year and 10-year OS rates were 88.8% and 85.1%, respectively, for standard-risk patients and 63.1% and 57.3%, respectively, for high-risk patients ($P < .001$). The 5-year and 10-year OS rates were 80.0% and 78.1%, respectively, for group I patients and 80.3% and 72.4%, respectively, for group II patients, with no OS difference by RT modality ($P = .93$) (Fig. 1). For patients with standard-risk disease, the 5-year and 10-year OS rates were 84.5% and 84.5%, respectively, in group I and 93.8% and 85.3%, respectively, in group II ($P = .55$). For patients with high-risk disease, the 5-year and 10-year OS rates were 68.5% and 63.2%, respectively, in group I and 56.1% and 49.9%, respectively, in group II ($P = .40$).

Secondary Malignant and Benign Neoplasms

Six SMNs were identified (4 in group I, 2 in group II). The 5-year and 10-year SMN incidence rates were 1.0% and 6.9%, respectively, after RT completion for all patients (Fig. 2A). The 5-year and 10-year SMN incidence rates were 0.0% and 8.0%, respectively, for group I and 2.2% and 4.9%, respectively, for group II ($P = .74$) (Fig. 2B). Table 2 indicates that there was no difference in the distribution of SMNs according to sex, age at RT (≤7 or >7 years), risk category, CSI dose (18.0-23.4 vs 30.6-39.6 Gy), RT modality, or type of CT (SJMB vs COG and other).

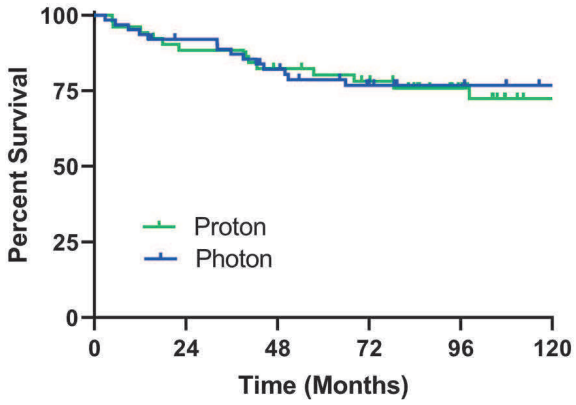

Figure 1. Overall survival rates are illustrated for all patients by treatment modality.

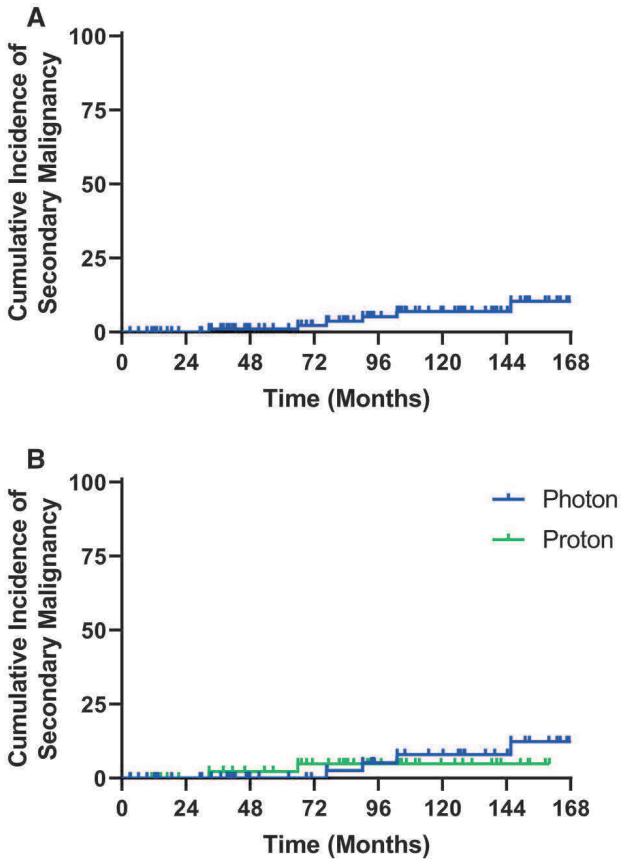

Figure 2. The incidence of secondary malignant neoplasm in 115 children with medulloblastoma is illustrated, including the cumulative incidence of secondary malignancy (A) for all patients and (B) by treatment modality.

TABLE 2. Distribution of Secondary Malignant Neoplasms According to Patient, Tumor, and Treatment Parameters

Parameter	No. of Patients		P^a
	SMN (n = 6)	No SMN (n = 109)	
Sex			.37
Male	3	77	
Female	3	32	
Age at RT, y			.44
≤7	2	56	
>7	4	53	
Risk category			.41
Standard	5	68	
High	1	41	
CSI dose, Gy			.40
18.0-23.4	5	65	
30.6-40.0	1	44	
RT modality			.69
Group I (photon)	4	59	
Group II (proton)	2	50	
Chemotherapy			1.00
SJMB96/ SJMB03	4	73	
COG/other	2	36	

Abbreviations: COG, Children's Oncology Group; CSI, craniospinal irradiation; Gy, gray; RT, radiotherapy; SJMB96/SJMB03, St Jude medulloblastoma studies 96 and 03, respectively; SMN, second malignant neoplasm.
[a]*P* values were determined using the Fisher exact test.

In 2 patients, the SMNs (malignant glioneuronal tumor, glioblastoma) were both in the cerebellum within the clinical target volume. The patient who developed a cerebellar glioblastoma had CHARGE syndrome, a condition associated with coloboma, heart defects, atresia choanae, growth retardation, and genital and ear abnormalities, but not secondary neoplasms. Two SMNs (a papillary thyroid cancer and a cardiac tumor) occurred within the exit dose region of the photon spinal field, and both received approximately 13 to 20 Gy to the affected organs. The cardiac tumor was never biopsied because of parental refusal. The patient received primarily supportive therapy for the cardiac tumor; however, by approximately 5 years after diagnosis of the SMN, the patient developed lung and liver metastases. One patient developed an intermediate grade mucoepidermoid carcinoma in the parotid gland at the entrance path of the proton beam. Another patient developed a mixed germ cell tumor in the testicle, which was outside the photon radiation field. Table 3 lists details of the 6 SMNs that developed among the 115 patients who received CSI. Of the 6 patients who developed an SMN, the 2 who developed an SMN in the cerebellum both died within 13 months of diagnosis of the SMN. Three patients were without evidence of disease at last follow-up after definitive treatment of an SMN, which included surgery with or without CT. The patient who had the unbiopsied cardiac tumor was alive with lung and liver metastases at last follow-up.

The timing of SMN diagnosis was from 32.6 months to 12 years after RT. It is interesting to note that both SMNs from group II patients occurred earlier at 32.6 and 65.9 months after RT, whereas the SMNs from group I patients occurred later, from 75 months to 12 years after RT.

None of the patients had a secondary meningioma or a secondary skin cancer. Two patients developed a secondary benign neoplasm, both with thyroid adenoma. Both secondary thyroid adenomas were seen in group I patients at 10.6 years and 12.5 years after completion of RT. Because both secondary benign tumors occurred after 10 years, the 5-year and 10-year rates of secondary neoplasms were the same as the 5-year and 10-year rates of SMN, with no difference according to RT treatment modality.

DISCUSSION

Modeling studies have previously reported an expected lower incidence of SMNs in children who receive PT compared with those who receive photon RT because the former results in a reduced volume of normal tissue exposed to radiation.[1-3,9] However, an increased total body dose secondary to neutrons from passively scattered protons has been observed, which potentially may yield more SMNs. Similarly, the use of IMRT may also be associated with a higher dose to the total body secondary to more monitor units, leakage radiation, and a larger volume of normal tissue exposed to low-dose radiation.[4,5,10] Therefore, we looked at the long-term follow-up of our children with medulloblastoma to see whether there were unusual trends for more SMNs.

In this study, we did not observe a difference in SMN incidence between the 2 groups with a median follow-up of 12.8 years for group I and 8.7 years for group II after RT completion. The 5-year and 10-year SMN incidence rates were 0.0% and 8.0%, respectively, for group I and 2.2% and 4.9%, respectively, for group II. There are some observations that are worth highlighting. First is the absence of secondary leukemias, which tend to occur within 7 years of treatment.[11] Because of the increased total body dose from neutrons in group II patients or from leakage radiation and low-dose bath in group I patients, there is concern that the bone marrow might be more susceptible to development of secondary leukemias. Second, in 2 of the 4 patients who

TABLE 3. Secondary Malignant Neoplasms in Patients Who Had Medulloblastoma Treated With Proton or Photon Radiotherapy

Patient No.	Sex	Age at RT, y	Risk Category: Treatment	RT Modality	Time to Develop SMN After RT, mo	Type of SMN	Location of SMN According to RT Fields	Estimated Mean Dose to Organ With SMN, Gy	Treatment for SMN	Outcome After SMN
1	Male	8.8	High risk: GTR followed by 34.2 Gy CSI + 54 Gy posterior fossa + SJMB96 CT	Photons	89	Malignant mixed germ cell tumor of the left testicle	Outside RT field	<0.1	Left orchiectomy and chemotherapy	Alive, NED 72 mo after dx of SMN
2	Male	10.2	Standard-risk: GTR followed by 23.4 Gy CSI, 36 Gy posterior fossa, 55.8 Gy tumor bed + SJMB96 CT	Photons	144	Papillary carcinoma of the thyroid gland	Exit dose region of PA spinal field	13	Thyroidectomy	Alive, NED 37 mo after dx of SMN
3	Female	4	Standard-risk: GTR followed by 23.4 Gy CSI, 36 Gy posterior fossa, 54 Gy tumor bed + SJMB96 CT	Photons	102	Low-grade sarcoma of the heart[a]	Exit dose region of the PA field	20	Supportive care for cardiac failure	Alive with disease 95 mo after dx of SMN
4	Female	10.5	Standard-risk: GTR followed by 23.4 Gy CSI + 54 Gy tumor bed + COG A9961 CT	Photons	75	Malignant glioneuronal tumor of the cerebellum	Within the target	54	Debulking	DOD 3 mo after dx of SMN
5	Male	5.5	Standard-risk: GTR followed by 23.4 Gy CSI + 54 Gy tumor bed +COG A9961 CT	Protons	65.9	Glioblastoma of cerebellum	Within the target	54	GTR and 54 Gy reirradiation	DOD 12.6 mo after dx of SMN
6	Female	7.1	Standard-risk: GTR followed by 23.4 Gy CSI + 55.8 Gy tumor bed + SJMB03 CT	Protons	32.6	Intermediate-grade mucoepidermoid carcinoma of left parotid gland	Within entrance dose of 1 of the beams	13	Parotidectomy	Alive, NED 105.6 mo after dx of SMN

Abbreviations: COG, Children's Oncology Group; CSI, craniospinal irradiation; CT, chemotherapy; DOD, died of disease; dx, diagnosis; GTR, gross total resection; Gy, gray; NED, no evidence of disease; PA, posterior/anterior; RT, radiotherapy; SJMB96/SJMB03, St Jude medulloblastoma studies 96 and 03, respectively; SMN, secondary malignant neoplasm.
[a]This sarcoma was not pathologically proven because the parents refused biopsy, but it was assumed secondary to evolution to distant metastases in liver and lungs.

received photons, the location of the SMN was in the exit dose region of the spinal field (thyroid cancer and unbiopsied cardiac tumor). A previous meta-analysis of patients with medulloblastoma showed that approximately one-half of the SMNs in patients who received photon RT for medulloblastoma occurred outside of the central nervous system and primarily in the exit dose region of the photon field, consistent with the findings of this study.[12] Third, the collective 10-year incidence of SMNs after RT in this study was 6.9% with a median follow-up of 12.8 years for photons and 8.7 years for protons. The COG A9961 trial of 379 patients who had standard-risk medulloblastoma reported a 10-year SMN incidence of 4.2% with a median follow-up of 9.7 years. In the meta-analysis of 1114 patients by Bavle et al, the 10-year SMN rate was 3.7% with a median follow of approximately 9 years.[12] The 10-year second neoplasm incidence for 2271 patients with medulloblastoma in the Surveillance, Epidemiology, and End Results (SEER) database for the years 1973 to 2014 was 3.1%.[13] In the Massachusetts General Hospital phase 2, single-arm study of 59 children with medulloblastoma, there were no SMNs at a median follow-up of 7 years.[14] The incidence rates of SMN detailed above are difficult to compare because follow-up times and treatments are different. The RT doses and treatment volumes as well as CT are also variable in these studies. In the COG A9961 study, the CSI dose was 23.4 Gy for all patients because the protocol was for standard-risk disease. The SEER 18 data included patients who received no RT, involved-field RT, and CSI. Higher RT doses and larger treatment volumes are associated with higher risks of SMN.[15] The SEER data also included approximately 30% adult patients, who are less likely to develop SMNs compared with children.[16] Others have suggested a higher SMN rate with the use of alkylating agents in addition to RT for medulloblastoma.[11,17] Finally, the OS rates were the same as those for patients with medulloblastoma in this study and were comparable to rates reported in the existing photon and proton literature, validating the efficacy of PT for this tumor.[11,14,17]

Whether the incidence of SMN after RT can be reduced by using passively scattered protons requires further study and longer follow-up. Chung et al performed a retrospective cohort study of 558 patients who received passive scatter PT at the Harvard Cyclotron matched by age, sex, year of treatment, histology, and site with 558 patients who received photons from the SEER data. Their study included children and adults with a variety of tumor types and treatment locations. The use of PT was associated with a reduced hazard ratio of 0.52 for the development of an SMN.[18] A recent National Cancer Database study of pediatric and adult patients with various different diagnoses showed that proton beam therapy had a lower risk of second cancer compared with 3DRT or IMRT. Limitations of that study included a low number of patients who received protons (1.3% of the entire National Cancer Database group) and a median follow-up of 5.1 years. Interestingly, despite the concern of increased body dose with IMRT, there was no difference in the SMN rate between those receiving 3DRT and those receiving IMRT.[19] Our study specifically looked at medulloblastoma in children who received CSI followed by a boost with multiagent CT. There was no difference in SMN rates in our patients with medulloblastoma according to RT treatment modality; however, the median follow-up is only 8.7 years for patients in group II. It is worth mentioning that both patients treated with PT who developed SMNs did so within 6 years after RT, and longer follow-up may reveal more cases. Another limitation of the study is the technique of photon CSI used in the study, which may not be as relevant today with the advent of volumetric arc therapy (VMAT). VMAT is able to confine CSI dose to the spine with less dose anteriorly in the thorax, abdomen, and pelvis. Treatment times are also faster compared with older methods of IMRT, with less leakage radiation. The disadvantage of the VMAT approach is a larger volume of normal tissue receiving low-dose RT, which may also translate to a higher SMN risk. This study is also limited to passively scattered protons and may not be as relevant to current proton CSI techniques, which use scanning beam protons. Passively scattered protons are thought to have 10 times higher doses at >20 cm distance from the field edge compared with IMRT.[10] Scanning beam protons, which are associated with less radiation outside the RT field compared with IMRT and passively scattered PT, may result in less SMNs.[10] Although we do not observe a reduction of SMNs in this analysis, we are reassured by the absence of secondary leukemias, which theoretically may be seen with higher body doses in children receiving IMRT or passively scattered protons. A previous report from the University of Florida showed a 5-year and 10-year second tumor risk of 0.6% and 1.7%, respectively, for 1713 children treated with passively scattered protons. Unlike our study, that study treated different types of tumors, including those outside the brain, with different RT fields and doses, with

or without CT, and excluded children with tumor predisposition syndromes.[20]

In 1 study from the St Jude-Washington University Pediatric Cancer Genome Project, 8.5% of children and adolescents had germline mutations identified in cancer predisposing genes.[21] We did not have any patients with a known tumor predisposition syndrome; however, as the Pediatric Cancer Genome Project reported, some of our patients probably have undetected mutations in cancer predisposing genes. It is a possible limitation of the current study because we do not know the proportion of patients with undetected mutations in groups I and II.

Our analysis demonstrates no difference in SMN incidence between group I and II patients at 10 years after RT. Our study is hypothesis-generating, in that we may have to use scanning beam protons to see a lower incidence of SMN in patients with proton-treated medulloblastoma. We continue to recommend PT in the treatment of medulloblastoma based on advantages in preservation of cognitive function and reduction of endocrinopathies in long-term survivors.[22,23]

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CONFLICT OF INTEREST DISCLOSURES

Arnold C. Paulino reports royalties from Elsevier for a textbook on radiotherapy planning outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Arnold C. Paulino: Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, and supervision. **Ethan B. Ludmir:** Methodology, formal analysis, data curation, and writing–original draft. **David R. Grosshans:** Investigation, resources, and writing–review and editing. **Jack M. Su:** Investigation, resources, and writing–review and editing. **Susan L. McGovern:** Investigation, resources, and writing–review and editing. **M. Fatih Okcu:** Investigation, resources, and writing–review and editing. **Mary Frances McAleer:** Investigation, resources, and writing–review and editing. **Patricia A. Baxter:** Investigation, resources, and writing–review and editing. **Anita Mahajan:** Investigation, resources, and writing–review and editing. **Murali M. Chintagumpala:** Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing–review and editing, and supervision.

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