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ONCOLOGY: RESEARCH ARTICLE

Development of second primary tumors and outcomes in medulloblastoma by treatment modality: A Surveillance, Epidemiology, and End Results analysis

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Abstract

Background: As treatment modalities for medulloblastoma have developed and overall survival (OS) has improved, there are relatively limited data on the impact of long-term effects such as risk of second primary tumors (SPT). To address the knowledge gap, we analyzed factors associated with the risk of SPT and OS by treatment modality for medulloblastoma.

Methods: We queried the Surveillance, Epidemiology, and End Results (SEER)-18 database for patients diagnosed with medulloblastoma in 1973-2014. Patients were then grouped by age, gender, race, geographic region, histology, adjuvant treatment (no radiation [RT] and no chemotherapy [CT], RT and CT, RT alone, or CT alone), era of diagnosis (1973-1994 or 1995-2014), and survival time. Cumulative incidence, factors associated with SPT and OS were analyzed.

Results: Of 2271 patients, 146 developed SPT, of which 42 were benign. The incidence of SPT was 3.1% and 4.9% at 10 and 15 years, respectively. The incidence of SPT was 3.1% with RT + CT versus 3.7% with RT alone at 10 years. The most common site for an SPT was the central nervous system. Female gender ($P = 0.01$) and longer OS of ≥21 years ($P < 0.01$) were associated with higher risk of SPT. RT + CT led to better OS than RT only (66.1% and 61.4% vs 55.6% and 49.7% at 10 and 15 years) ($P < 0.01$).

Abbreviations: BCCSS, British Childhood Cancer Survivor Study; CCSS, Childhood Cancer Survivor Study; CI, confidence interval; CNS, central nervous system; CSI, craniospinal irradiation; CT, chemotherapy; GI, gastrointestinal; IMRT, intensity-modulated radiotherapy; OR, odds ratio; OS, overall survival; RT, radiation; SEER, Surveillance, Epidemiology, and End Results; SHR, subdistribution hazard ratio; SMN, second malignant neoplasm; SPT, second primary tumor.

Conclusions: Medulloblastoma patients have a relatively low risk of SPT at 10 years with treatment. Use of RT + CT led to better OS with no statistical difference in SPT compared with the RT alone.

KEYWORDS
chemotherapy, medulloblastoma, radiotherapy, second primary tumor, survival

1 | INTRODUCTION

Medulloblastoma is one of the most common central nervous system (CNS) malignant neoplasms in children with an incidence rate of 6.0 per million in patients 1-9 years old, which is 10 times higher than in adults.[1] After maximal safe resection of tumor, craniospinal irradiation (CSI), followed by a boost to the posterior fossa tumor bed, is an essential component of treatment for medulloblastoma.[2,3] Because CSI involves large radiation fields, exposure of normal tissues to radiation results in potential acute and late toxicities to several organ systems.[4,5] One form of radiation-induced late effects is the development of a second primary tumor (SPT).[6-8] Radiotherapy (RT) dose, the organs exposed to RT, and patient characteristics have all been correlated with the development of SPT.[8,9]

In the past three decades, chemotherapy (CT) has also been incorporated into the management of childhood medulloblastoma, with a reduction of CSI dose from 36 to 23.4 Gy for standard-risk patients.[10,11] Similarly, improvements in neuroimaging and radiotherapy dose delivery have reduced the volume that requires an additional radiation boost after CSI, from coverage of the entire posterior fossa to the tumor bed with a margin.[12-15] For patients < 3 years old who are the most vulnerable to radiation-related toxicity effects, delaying or omitting radiation is an option to be considered.[16,17] For children ≥ 3 years old, using proton beam therapy for CSI rather than photons will reduce dose to surrounding normal organs because of proton's lack of an exit dose and maybe beneficial in the reduction of late effects.[18,19]

Although the current event-free survival rates for standard-risk and high-risk groups exceed 80% and 65% at five years, potential late treatment effects such as SPT could cause late mortality in these survivors. Importantly, both systemic treatment and radiation could increase the risk of SPT.[20,21] Little is known regarding the subsequent risk of SPT by treatment modality among these long-term survivors on a population-based level.[2,10,22,23] Additionally, analyses of SPT can be challenging because of the long follow-up periods needed and the relatively low incidence of SPT.

The Surveillance, Epidemiology, and End Results (SEER) database provides information on treatments for large populations, long-term outcomes, and incidence of SPT over decades. Therefore, we sought to analyze and compare incidence rates and risk factors for developing SPT among patients treated for medulloblastoma and the long-term overall survival (OS) among different treatment modalities. Our hypothesis was that the risk of SPT could differ by age, gender, year of diagnosis, length of OS, and type of adjuvant treatment. Furthermore, OS could be different by adjuvant treatment groups.

2 | METHODS

We queried the SEER-18 tumor registry from SEERS*stat software version 8.3.5 to identify patients diagnosed with medulloblastoma (not otherwise specified [ICD-O-3 = 9740/3], desmoplastic [ICD-O-39471/3], or large cell [ICD-O-3 = 9474/3]) diagnosed from 1973 through 2014 with the first malignancy ever diagnosed being a medulloblastoma. Patients with unknown RT status or those who received nonexternal-beam radiation (e.g., radioactive isotopes or implants) were excluded. Cases with unknown or no survival time were also excluded. Patient demographics, vital status, survival time, receipt of RT, receipt of CT, year of diagnosis, development of SPT, type of SPT, time interval to SPT, and survival time after SPT were obtained for analysis. A second diagnosed tumor in the SEER sequence code, which was not medulloblastoma, was defined as an SPT in order to differentiate a secondary treatment-associated tumor from a relapse of the original medulloblastoma tumor. Methods used for SPT diagnosis per SEER data included histology, cytology, microscopic confirmation, imaging (i.e., CT, MRI, and ultrasound/sonography), laboratory tests or tumor marker, surgeon's operative report, gross autopsy findings or clinical diagnosis only. In our cohort, patients with at least one SPT were included and an individual could have more than one SPT. Cases were analyzed by their diagnosis of the first SPT only. For time-to-event analyses, individuals were censored after they experience their first event or diagnosis of an SPT. We by definition did not include the relapse of medulloblastoma as an SPT.

We further classified patients according to age at diagnosis of medulloblastoma (0-10 years, 11-20 years, or ≥21 years), gender (male or female), race (white, black, or other), era of diagnosis (1973-1994 or 1995-2014), survival time from the diagnosis of medulloblastoma (0-10 years, 11-20 years, or ≥21 years), type of adjuvant treatment (no RT and no CT, both RT and CT, RT only, and CT only), and tumor histology (desmoplastic nodular, large cell, or not otherwise specified). In addition, we further classified SPT into benign (e.g., meningiomas) and malignant tumors according to ICD-O-3 and also consensus decision from at least three radiation oncologists (CN, AP, DNY) by reviewing all histology types. In general from SEER reporting, ICD-O-3 group 0, 1, and 2 were considered as benign, whereas ICD-O-3 group 3 was considered malignant with the exception of "refractory anemia," "therapy-related myelodysplastic syndrome," and "refractory thrombocytopenia," which the reviewing oncologists favored to be clinically more benign than malignant tumors.

Cumulative incidence of SPT was analyzed with a competing-risk analysis accounting for the competing risk of death. To compare

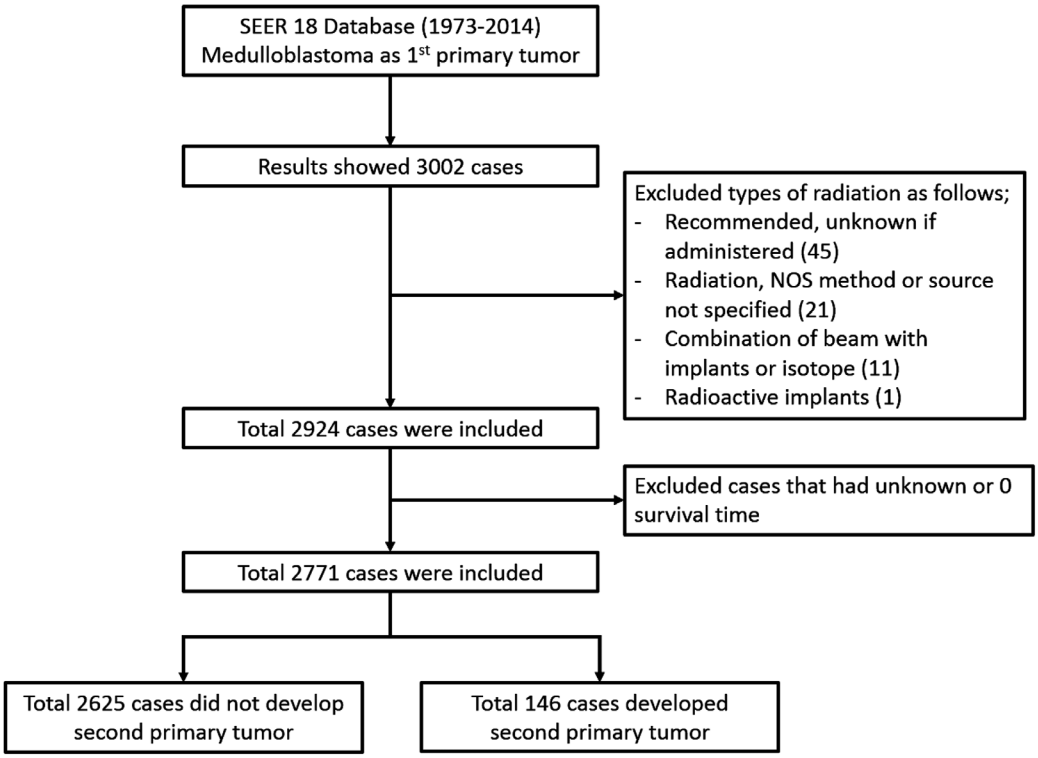

FIGURE 1 Consort diagram

incidence rates between groups, a Fine and Gray's subdistribution hazard model was performed for examining factors associated with developing SPT. Chi-square tests, simple logistic regression, and multivariable logistic regression were used to analyze the risk of developing SPT according to the factors noted above. Covariates potentially associated with risk of SPT on univariable analyses ($P < 0.2$) were selected for the multivariable model with forward model selection. Treatment episode along with the selected significant covariates ($P < 0.05$) remained in the final model. The location of SPT was documented with descriptive statistics. OS rates were estimated by the Kaplan-Meier method, with subgroups compared using log-rank tests. For concise presentation, the chi-square, sensitivity analyses, additional OS analyses, and the comparative analysis between the competing-risk model and the cumulative incidence model without adjusting for competing risk are included in Supporting Information.

3 | RESULTS

We identified 2771 patients with medulloblastoma in the SEER-18 database, of whom 146 developed SPT: 42 were benign and 104 were malignant. Patient, tumor and treatment characteristics were then analyzed according to development of SPT (Figure 1).

3.1 | Cumulative incidence rates of SPT

Of the 2771 identified patients, 146 (5.27%) developed SPT, of which 42 were benign tumors (1.52% of all identified patients and 28.77% of all SPT). Out of 146 cases, there were 126 cases that developed one SPT, 18 cases that developed two SPTs, one case that developed three SPTs, and one case that developed four SPTs. Median latency of developing the first SPT was 12.5 years, 17.2 years, and 9.7 years for the SPT cohort, patients who developed a benign SPT, and patients who had a malignant SPT. It was 16.9 years, 11.8 years, 3.8 years, and 6.7 years for patients who received RT only, both RT and CT, CT only and no RT and CT groups, respectively. Overall incidence rates of SPT were 3.1% (95% confidence interval [CI] 2.4-4.0) at 10 years and 4.9% (95% CI 4.0-6.1) at 15 years (Table 1 and Figure 2A). No statistically significant difference in cumulative incidence rates was found between patients receiving RT only versus RT + CT (3.7% vs 3.1% at 10 years or 5.9% vs 4.9% at 15 years) ($P = 0.31$) in competing-risks analysis (Figure 2B), and that lack of difference was also consistent in the Fine and Gray's competing-risk regression model analysis (RT vs RT + CT, subdistribution hazard ratio [SHR] 1.19, 95% CI 0.85-1.68, $P = 0.31$) (Table 1). Additional multivariable adjusted models continued to show not statistical differences (Supporting Information Table S3 and Supporting Information Figure S1).

3.2 | Risk of developing SPT

Chi-square tests revealed significant differences in the overall crude SPT rates based on patient age, gender, era of diagnosis, and treatment modality. Patients aged 11-20 years at diagnosis of medulloblastoma had the highest rate of SPT (7.1%) compared with patients 0-10 years old (4.4%) ($P = 0.04$) (Table 2). Female patients (6.6%) were more likely to develop SPT than male patients (4.4%) ($P = 0.01$). Patients whose medulloblastoma was diagnosed before 1995 had more SPTs

TABLE 1 SPT incidence by competing-risk analysis

	Cumulative incidence estimation	95% CI	*P* value
Overall (*N* = 2771)			N/A
10 years	3.10%	2.39%-3.99%	
15 years	4.90%	3.97%-6.10%	
20 years	7.10%	5.75%-8.67%	
CIF comparison (RT + CT vs RT only)			0.31
RT + CT (*N* = 1577)			
10 years	3.10%	2.24%-4.22%	
15 years	4.90%	3.66%-6.66%	
20 years	7.00%	5.36%-9.22%	
RT only (*N* = 694)			
10 years	3.70%	2.63%-5.07%	
15 years	5.90%	4.45%-7.70%	
20 years	8.30%	6.35%-10.90%	
	Fine and Gray's competing-risk estimation SHR	**95% CI**	***P* value**
RT + CT	1.00		
RT only	1.19	0.85-1.68	0.31

CT, chemotherapy; RT, radiation therapy; SHR, subdistribution hazard ratio; SPT, second primary tumor.

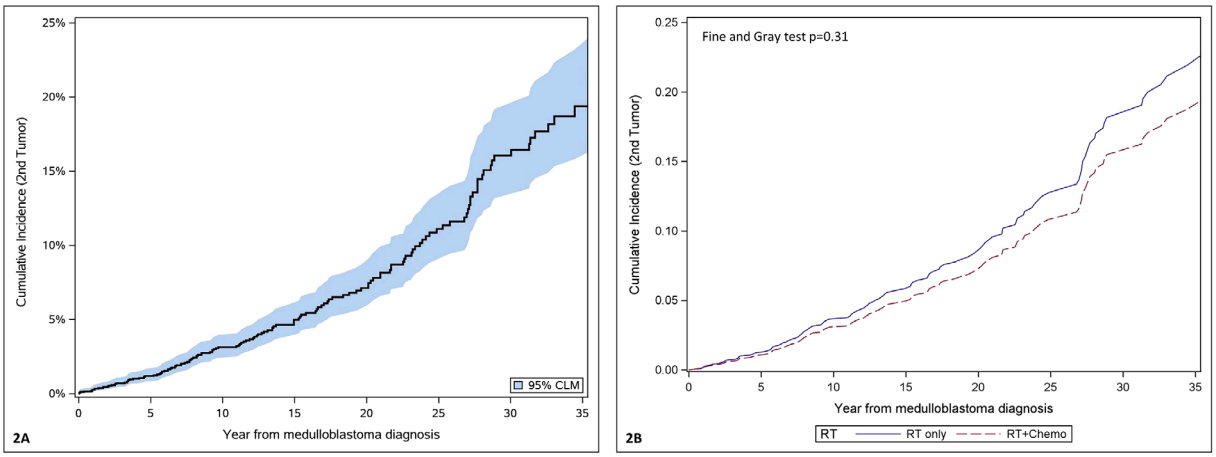

FIGURE 2 Cumulative incidence rates of SPT by competing risk. A, Overall cumulative SPT incidence among all patients with medulloblastoma. B, SPT cumulative incidence function estimate by competing-risk survival analysis with Fine and Gray's test for patients who received radiation (RT, blue line) and those who received RT and chemotherapy (CT, red line)

than those with a diagnosis in 1995-2014 (10.5% vs 3.3%, $P < 0.01$). Patients with longer OS after diagnosis with medulloblastoma had more SPTs than those living 10 years or less ($P < 0.01$). The SPT rate for patients living ≥ 21 years was 6.6%, whereas for those living 11-20 years and 0-10 years, these were 1.4% and 0.8%, respectively. Patients who received RT only had the highest percentage of SPT (9.5%), followed by patients given both RT and CT (4.3%), no RT and no CT (2.5%), and CT only (2.4%).

Simple logistic regression analyses revealed significant differences in the rate of SPT by age, gender, treatment modality, year of diagnosis, and length of survival after diagnosis. The odds ratio [OR] for developing SPT for 11-20-year-old vs 0- to 10-year-old was 1.67 (95% CI 1.10-2.54, $P = 0.02$), for female vs male was 1.53 (95% CI 1.10-2.14, $P = 0.01$), for diagnosis in 1995-2014 vs 1973-1994 was 0.29 (95% CI 0.20-0.40, $P < 0.01$), for patients surviving ≥ 21 years vs 0-10 years was 9.21 (95% CI 2.92-29.04, $P < 0.01$). Regarding treatment modalities, OR for no therapy vs RT only was 0.24 (95% CI 0.10-0.61, $P < 0.01$), for RT + CT vs RT only was 0.43 (95% CI 0.30-0.61, $P < 0.01$), and for CT only vs RT only, it was 0.23 (95% CI 0.10-0.51, $P < 0.01$). On multivariable logistic regression analysis, only gender, year of diagnosis, and survival time remained significant factors for developing SPT, with females at higher risk than males (OR 1.56, 95% CI

TABLE 2 Analysis of patient and treatment factors associated with development of SPT

	All	Developed SPT					Univariable model			Multivariable model		
		Yes		No								
	N	*N*	%	*N*	%	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
All cases	2771	146	5.3	2625	94.7							
Age at diagnosis, years						0.04			0.04			
0-10	1525	67	4.4	1458	95.6		1.00					
11-20	504	36	7.1	468	92.9		1.67	1.10-2.54	0.02			
≥21	742	43	5.8	699	94.2		1.34	0.90-1.98	0.15			
Gender									0.01			0.01
Male	1715	76	4.4	1639	95.6	0.01	1.00			1.00		
Female	1056	70	6.6	986	93.4		1.53	1.10-2.14	0.01	1.56	1.11-2.19	0.01
Race						0.14			0.15			
White	2317	114	4.9	2203	95.1		1.00					
Black	219	17	7.8	202	92.2		1.63	0.96-2.76	0.07			
Other	235	15	6.4	220	93.6		1.32	0.76-2.30	0.33			
Year of diagnosis						<0.01			<0.01			<0.01
1973-1994	769	81	10.5	688	89.5		1.00			1.00		
1995-2014	2002	65	3.3	1937	96.8		0.29	0.20-0.40	<0.01	0.34	0.23-0.49	<0.01
Treatment						<0.01			<0.01			0.20
RT only	694	66	9.5	628	90.5		1.00			1.00		
No RT, no CT	203	5	2.5	198	97.5		0.24	0.10-0.61	<0.01	0.49	0.19-1.25	0.13
RT + CT	1577	68	4.3	1509	95.7		0.43	0.30-0.61	<0.01	0.75	0.50-1.13	0.17
CT only	297	7	2.4	290	97.6		0.23	0.10-0.51	<0.01	0.52	0.23-1.19	0.12
Region						0.40			0.41			
Northeast and Mid-Atlantic	403	24	6.0	379	94.0		1.00					
South	362	14	3.9	348	96.1		0.64	0.32-1.25	0.19			
West	1583	81	5.1	1502	94.9		0.85	0.53-1.36	0.50			
Midwest	423	27	6.4	396	93.6		1.08	0.61-1.90	0.80			
Tumor histology						0.19			0.24			
Desmoplastic nodular	297	13	4.4	284	95.6		1.00					
Large cell medulloblastoma	80	[a]	[b]	[b]	[b]		0.28	0.04-2.15	0.22			
Not otherwise specified	2394	132	5.5	2262	94.5		1.28	0.71-2.28	0.41			
Survival time, years						<0.01			<0.01			<0.01
0-10	392	3	0.8	389	99.2		1.00			1.00		
11-20	282	4	1.4	278	98.6		1.87	0.41-8.40	0.42	1.94	0.43-8.78	0.39
≥21	2097	139	6.6	1958	93.4		9.21	2.92-29.04	<0.01	8.37	2.63-26.61	<0.01

CT, chemotherapy; CI, confidence interval; OR, odds ratio; RT, radiation therapy; SPT, second primary tumor.

[a] *N* < 3 suppressed per SEER agreement

[b] Suppression of *N* or % due to an associated small *N*.

1.11-2.19, *P* = 0.01 on adjusted analysis). Diagnosis during 1995-2014 was associated with a lower risk of SPT compared with diagnosis during 1973-1994 (OR 0.34, 95% CI 0.23-0.49, *P* < 0.01). Patients surviving ≥ 21 years corresponded to a higher risk of SPT compared with those living less than 11 years (OR 8.37, 95% CI 2.63-26.61, *P* < 0.01). Compared with RT only, receipt of RT + CT did not confer a statistically significant difference in SPT on adjusted analysis (OR 0.75, 95% CI 0.50-1.13, *P* = 0.17). These results are summarized in Table 2.

3.3 | Types of SPT developed

Among patients who developed SPT, the most frequent site was the CNS in 63 (43.2%) followed by endocrine and hematological systems, summarized in Supporting Information Table S4. The predominant histology diagnoses for the most common SPT disease sites were meningioma and glioma for CNS (*N* = 59); papillary, oxyphilic, or medullary carcinoma for endocrine sites (*N* = 19), and myeloid leukemias or lymphoblastic leukemias for hematologic sites (*N* = 14). This information

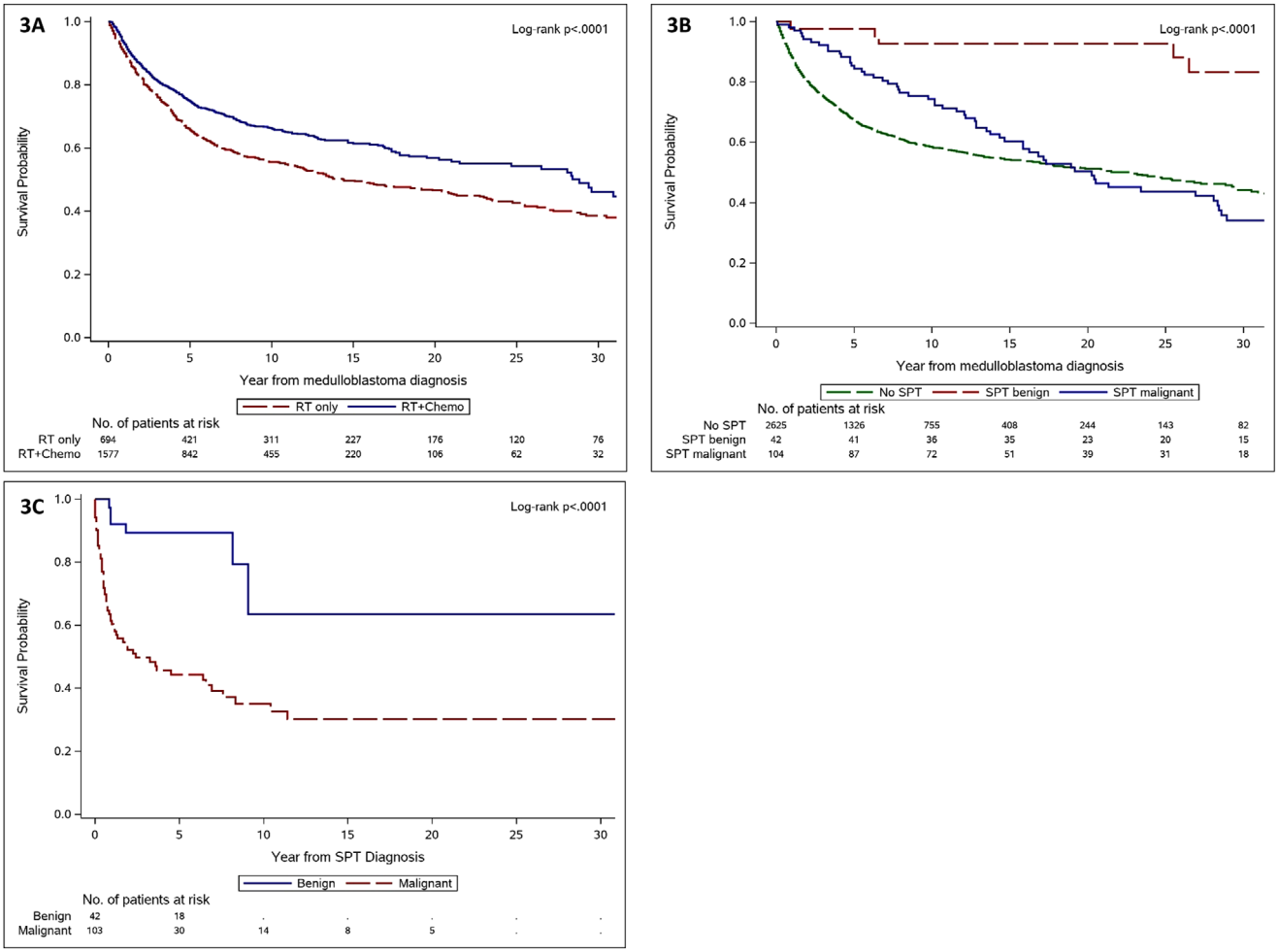

FIGURE 3 Overall survival. A, Overall survival from the diagnosis of medulloblastoma of patients who received either radiation only (RT, red line) or RT and chemotherapy (CT, blue line). B, Overall survival from the diagnosis of medulloblastoma of patients who have benign (red line), malignant (blue line) second primary tumor, and none-SPT (green line). C, Post-SPT survival of patients who have benign (blue line), malignant (red line) second primary tumor

is summarized in Supporting Information Table S5, along with the definition of benign and malignant SPT by histology codes. Among patients who received RT + CT and developed CNS SPT, 19 were malignant and 14 were benign. Among those receiving RT alone, 10 CNS SPTs were malignant and 17 were benign, and for those receiving chemotherapy alone, all three were benign (Figure 4). The next most common sites for SPT were endocrine in 18 (12.3%), hematological in 15 (10.3%), and gastrointestinal (GI) systems in 13 (8.9%). SPT in the CNS was more common in younger patients (55.2% for 0-10 years, 44.4% for 11-20 years, and 23.3% for ≥21 years). Females had a higher rate of breast SPT (8.6%), whereas males had higher head and neck SPT (4.0%) (Supporting Information Table S4). The information of SPT sites by gender and age group is summarized in Supporting Information Figure S2-S3.

CNS was also the most common location of SPT among patients given RT only (40.9%) and those given both RT and CT (48.5%). For patients given CT only, the CNS and the hematological systems were both the most common sites for SPT (42.9% and 42.9%). For patients who received no RT and no CT, the breast was the most common site for SPT (40%) (Figure 4).

3.4 | SPT overall survival

Because the risk of SPT could be dependent on whether patients received appropriate therapy and lived long enough to develop an SPT, we also assess the OS rates of patients. Median survival and OS rates at 10 and 15 years for patients who received RT + CT were 28.8 years, 66.1%, and 61.4%; all of which were significantly higher than for patients who received RT only (14.4 years, 55.6%, and 49.7%) ($P < 0.01$) (Figure 3A and Supporting Information Table S2). Secondly, the median survival and OS rates at 10 years for patients who received RT were 23.8 years and 62.5%, which were significantly higher than for patients who did not receive RT (seven years and 46.9%, $P < 0.01$) (Supporting Information Table S2).

The median overall survival from initial diagnosis with medulloblastoma for patients diagnosed with malignant SPT was 20.3 years and five-year OS 84.4% in comparison with a median survival of 40.4 years and five-year OS of 97.6% for patients diagnosed with benign SPTs. In contrast, the median survival was 22.75 years and five-year OS 67.4% for patients who did not develop SPT ($P < 0.01$) (Supporting

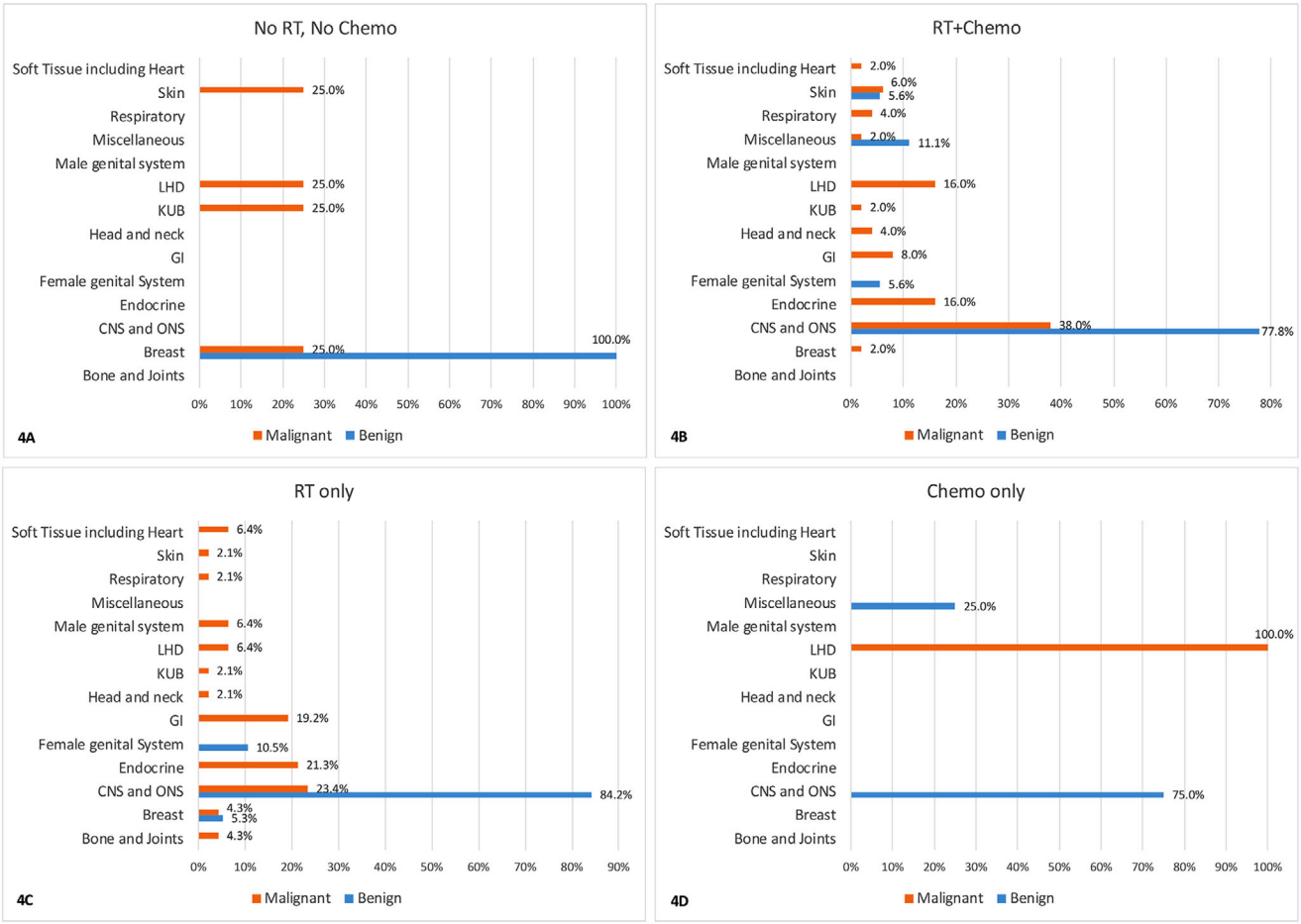

FIGURE 4 Sites of SPT by treatment received. A, Sites of SPT in no radiation (RT) and no chemotherapy (CT) group. B, Sites of SPT in both the RT and CT groups; C, sites of SPT in the RT-only group. D, Sites of SPT in the CT-only group

Information Table S1 and Figure 3B). From the time of diagnosis with a secondary primary tumor, the median survival was 2.4 years and five-year OS 44.3% for those diagnosed with a malignant SPT. In contrast, for those diagnosed with a benign SPT, such as meningioma, they had longer survival with a median survival not reached during the follow-up period and five-year OS of 89.3% ($P < 0.01$) (Supporting Information Table S1 and Figure 3C).

4 | DISCUSSION

Because of the higher cure rates in medulloblastoma with the current multimodality approach, the prevention of late complications of treatment has increasingly been important. In our study, patients diagnosed with medulloblastoma had a low risk of SPT of 3.1% at 10 years. Secondly, the risk of SPT does not significantly differ between the era of RT alone versus combined RT and chemotherapy at 10 years at 3.1 vs 3.7%. Lastly, regardless of SPT risk, adjuvant therapy is warranted because patient survival outcomes are improved in the current era of RT + CT in comparison with RT alone.

In this review of the SEER-18 database, the 10- and 15-year rates of SPT with adjuvant chemoradiation were 3.1% and 4.9%. A recent report from the Children's Oncology Group A9961 of standard-risk medulloblastoma children treated with RT and one of two CT regimens (cisplatin, vincristine plus either CCNU or cyclophosphamide) showed a 10-year incidence of second malignant neoplasm (SMN) of 4.2%.[24] Despite longer follow-up time and including both benign and malignant tumors, the SPT incidence of our study is lower than that from COG. The COG study included only malignant tumors. This finding could be explained by the fact that all patients in that COG study received adjuvant radiation and chemotherapy and it reflects a select trial population. In comparsion, our population-based study reflects the larger cohort of patients diagnosed with medulloblastoma, including those who received neither radaition nor chemotherapy. For instance, in our analysis, those patients receiving no RT and no CT had the lowest risk of SPT as well as lowest survival. A second possibility is regarding the field of radiation. No information on treatment filed is available in the SEER database. Thus, although all patients of COG group received CSI, it is possible a small minority of patients in our cohort who were coded as receiving RT among the RT-only group and RT + CT group could have received either focal RT or palliative doses. A third posibility is data from SEER does not routinely collect nonmelanoma skin cancer, a common radition-related cancer,[25,26] while in contrast basal cell carcinoma was also reported as a second primary tumor in COG.

In a previous population-based study from the Connecticut (1935-1992), SEER (1973-1992), and Swedish Cancer Registries (1958-1992), a 5.4-fold excess of SMN was seen in medulloblastoma patients based on 20 observed and 3.7 expected cancers. Of the 14 SMN where treatment information was known, only one was reported to have received RT and CT with the rest receiving RT alone after resection.[7] The recent data from the SEER 9 tumor registry (1973-2014) also showed 4.49-fold excess of SMN in medulloblastoma patients.[27] In a report from the Childhood Cancer Survivor Study (CCSS) for different pediatric tumors, the risk of subsequent neoplasm risk was examined according to decade of treatment in survivors of childhood cancer. It was noted that the 15-year cumulative incidence of SMN was 2.1% in the 1970s, 1.7% in the 1980s, and 1.3% in the 1990s. The authors found that the decrease of SMN according to decade was correlated with the use of less RT (77% in 1970s, 54% in the 1980s, and 33% in the 1990s) as well as a lowering of the median RT dose of 30 Gy in the 1970s to 26 Gy in the 1990s.[9] With the current approach of decreasing CSI doses from 36 to 23.4 Gy in standard-risk patients and use of a tumor bed instead of entire posterior fossa boost with the addition of CT, one would hypothesize that the rate of SPT may be lower because RT dose to the craniospinal axis is less in more than half of the patients and a smaller volume of brain tissue is getting the RT boost.

However, on the other hand, the use of multiagent chemotherapy may also contribute to a higher risk of SPT when combined with RT. Three previous studies with short follow-up have raised early concerns that the rate of SPT might be higher than historically when RT alone was used.[24,28,29] In this SEER study, the rate of SPT among 1577 patients who received CT and RT and 694 patients who received RT alone was not statistically different (3.1 vs 3.7% at 10 years, $P = 0.31$) on competing-risk analysis. The competing-risk model takes into account and adjusts for the competing risk of death, which changes the population at risk of developing SPT. It also takes into account the additional length of survival for patients who may go on to develop an SPT. Generally speaking, models not accounting for competing risk may overestimate the rate of an event.[30] On adjusted analysis taking into account length of survival among clinical or demographic covariates, the slightly lower odds ratio of developing an SPT with the use of CT and RT in comparison with RT alone did not reach statistical significance (OR 0.75, 95% CI 0.50-1.13, $P = 0.17$). In a smaller study from St. Jude Children's Research Hospital ($n = 237$) and CCSS ($n = 139$), there was no difference in the cumulative incidence of SPT (12% vs 11.3% at 20 years, $P = 0.44$) among medulloblastoma patients who received CT and RT versus RT alone.[29] It is interesting to note that medulloblastoma patients treated at the latter part (1995 to 2014) had a lower percentage of SPT compared with those treated in the earlier part of the study (1973 to 1994). In addition to reducing radiation dose and target volume, there was improvement of radiation techniques in the latter era. For instance, current proton and intensity-modulated radiotherapy (IMRT) would both possibly reduce the risk of developing SPT. Proton beams could reduce exit dose to normal organs and IMRT could conform dose to the target volume and lower high dose to normal organs.

In this population-based study, the most common location for an SPT was the CNS. This is similar to the findings of the CCSS and the British Childhood Cancer Survivor Study (BCCSS) and not surprising because the entire brain and the spinal axis is the RT target during CSI.[9,31] It is interesting that this was true for all patients receiving adjuvant treatment with the exception of those that got CT only, where both CNS and the hematological systems were both predominant sites of SPT.

Next, the second key focus of our study was to assess the risk of SPT during the era of "RT alone" to the era of "RT + CT." For a few decades, standard-risk patients could receive lower doses of CSI from 36 Gy to 23.4 by receiving concomitant chemotherapy.[3,10,13] We hypothesized that the risk of SPT could be less in this group. However, our study did not show statistical differences in SPT risk between the RT-alone and RT + CT groups. One explanation is that although RT + CT reduces the solid malignancy risk of SPT, it may possibly also slightly increase the hematologic risk of SPT. Also, SPT risk is likely dose dependent, and the RT dose and dose or cycles of chemotherapy are not available in SEER. One limitation is that we could not imply that all patients in the RT + CT group had standard-risk medulloblastoma and receive chemotherapy to reduce CSI dose. Because the radiation dose was not provided in SEER data, some patients in the RT + CT group could have had high-risk disease (e.g., spinal seeding, large residual tumor) and would receive nonreduced dose CSI (36 Gy), not different from the RT-only group. In addition, the sequence of RT and CT was not provided. Some patients in the RT + CT group might not have received concomitant chemoradiation with reduced CSI dose. They might have received CT to delay the full-dose CSI in very young patients or might receive RT only as the adjuvant treatment but eventually received CT when disease recurred. Therefore, these possibilities could impact our results. However, even though SPTs of RT only and RT + CT were not statistically different, the percentage of SPT for RT alone was slightly higher than RT + CT.

Third, from our findings, the risk of SPT significantly increased in the longer survival time groups. This finding could be explained because these survivors lived long enough to develop SPT. From previous studies, the latency period for developing leukemia was about 5-10 years, and for solid tumor it was 10-60 years after radiation, which could cause DNA base damage and impairment of DNA repair proteins. Consequently, this would lead to mutations and malignant transformation, which typically present in later years.[32] Our study also reported the survival of patients who developed benign SPT, malignant SPT, and who did not develop an SPT. The 10- and 15-year OS were shortest in those not developing an SPT. This finding could be explained by survival bias. Because the development of an SPT requires a latency period, patients in the "no SPT" group could have had too short a survival time to develop SPT (Supporting Information Table S1). Secondly, more patients who did not develop an SPT received neither RT nor chemotherapy. There are confounding factors that could contribute to why some patients do not receive therapy. Although a small number of patients who did develop an SPT and did not receive therapy had a high survival, these findings further highlight the issue that it is longer survival in general that places patients at risk for SPT.

Similarly, patients receiving RT alone had among the highest median follow-up, likely reflective of the fact that more of those patients were diagnosed in the earlier era. Lastly, we addressed adjusting for diagnosis era and treatment management in our multivariable logistic regression, which identified survival to be one of the strongest predictors of the development of SPT. Nevertheless, as a combined cohort, patients who received adjuvant treatment still had better OS compared with those who did not receive adjuvant treatment.

Finally, regardless of other confounding factors, patients treated with RT + CT had better 10- and 15-year OS rates (66.3% and 61.4%) compared with those treated with RT alone (55.6% and 49.5%, $P < 0.01$). Although randomized trials comparing RT with and without CT have been limited, a previous European study showed a better event-free and OS in patients with nonmetastatic medulloblastoma receiving the addition of CT.[3,23] Our study supports that although the risk of SPT for medulloblastoma patients may be low in the current era, the use of RT + CT still provides a higher survival benefit.

Although this study provides significant insight about risk factors, SPT incidence rates, and OS in patients treated for medulloblastoma, it had some limitations that are inherent in all observational studies. First, the radiation dose, type and completion of chemotherapy, and sequence of RT and CT were not readily available in the SEER database. Second, the RT fields and type of radiation (photons vs protons) were not available over the extensive follow-up period. We assumed that very young patients (< 3 years) would have received involved-field RT only (tumor bed and residual tumor) if RT was delivered, and that the rest of irradiated patients (≥ 3 years) had CSI. We also assumed that starting in the mid-2000s, some of the patients would have received proton therapy, which may be associated with less late effects such as SPT. The strength of our study is our analysis took into account differences in diagnosis and survival time by adjusting for the length of survival. A competing-risk analysis to adjust for differences in survival and censorship was performed. Importantly, this study was obtained from a large population database with long-term follow-up and long-term outcomes, which is essential for reporting SPT.

In conclusion, this large population-based database identified a 10- and 15-year SPT rate of 3.1% and 4.9% for patients diagnosed with medulloblastoma. Although the cumulative SPT incidence in patients with medulloblastoma who receive RT and CT compared with those receiving RT alone was slightly lower, it was not statistically different in either competing-risk analyses or multivariable regression analyses adjusting for clinical factors. Even though adjuvant treatment could cause SPT, our study showed that treatment with RT and CT + RT over the decades still significantly outweighs the potential side effects. Future prospective or retrospective matched-pairs studies with dose volume histograms of normal organs are needed to determine whether the SPT incidence would be lower with the use of proton beam compared with photon RT in patients treated for medulloblastoma. It would also be of interest to assess whether the incidence of SPT differs in varying molecular subtypes, which might provide insights into deescalating dose and field of radiation, in the prognostically better subgroups of molecular variants.

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CONFLICTS OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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