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Incidental Detection of Late Subsequent Intracranial Neoplasms with Magnetic Resonance Imaging Among Adult Survivors of Childhood Cancer

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Abstract

Purpose—Survivors of childhood cancer are at increased risk of developing subsequent neoplasms. In long term survivors of childhood malignancies treated with and without cranial radiation therapy (CRT), undergoing unenhanced magnetic resonance imaging (MRI) of the brain, we estimated detection of intracranial neoplasms.

Methods—To investigate neurocognitive outcomes, 219 survivors of childhood cancer underwent unenhanced screening MRI of the brain. 164 of the survivors had been treated for acute lymphoblastic leukemia (ALL) (125 received CRT), and 55 for Hodgkin lymphoma (HL) (none received CRT). MRI examinations were reviewed and systematically coded by a single neuroradiologist. Demographic and treatment characteristics were compared for survivors with and without subsequent neoplasms.

Results—Nineteen of the 219 survivors (8.7%) had a total of 31 subsequent intracranial neoplasms identified by neuroimaging at a median time of 25 years (range 12–46 years) from diagnosis. All neoplasms occurred after CRT, except for a single vestibular schwannoma within the cervical radiation field in a HL survivor. The prevalence of subsequent neoplasms after CRT exposure was 14.4% (18 of 125). By noncontrast MRI, intracranial neoplasms were most suggestive of meningiomas. Most patients presented with no specific, localizing neurological complaints. In addition to the schwannoma, six tumors were resected based on results of MRI screening, all of which were meningiomas on histologic review.

Conclusion—Unenhanced brain MRI of long-term survivors of childhood cancer detected a substantial number of intracranial neoplasms. Screening for early detection of intracranial neoplasms among aging survivors of childhood cancer who received CRT should be evaluated.

Implications for Cancer Survivors—The high prevalence of incidentally detected subsequent intracranial neoplasms after CRT in long-term survivors of childhood cancer and the minimal symptoms reported by those with intracranial tumors in our study indicate that brain MRI screening of long-term survivors who received CRT may be warranted. Prospective studies of such screening are needed.

Keywords

Survivors of Childhood Cancer; Cranial Radiation Therapy; Subsequent Intracranial Neoplasms; Meningiomas

Introduction

In the modern era of cancer treatment, more than 80% of those diagnosed with a pediatric malignancy will become five-year survivors.[1] This progress has resulted in a growing population of adult survivors of childhood cancer, with current estimates indicating that one in every 640 young adults between the ages of 20 and 39 is a survivor of a childhood malignancy.[2]

Survivors of childhood cancer are known to be at significant risk of developing subsequent neoplasms.[3-6] The risk of developing subsequent neoplasms associated with the central nervous system (CNS) is increased for survivors treated with cranial radiation therapy (CRT).[4,5,7-9] While some CRT-related subsequent intracranial neoplasms are high-grade malignancies, those with a late onset are mostly meningiomas among survivors of childhood (ALL).[8,10,11] The risk for meningioma appears to increase with attained age.[4,5,12] There are currently, however, no established guidelines for screening and early identification of subsequent CNS-associated neoplasms in survivors of childhood cancer who received CRT because prospective controlled trials evaluating the benefits, risks, costs and other factors associated with screening of survivors have not yet been conducted.[13,14]

Magnetic resonance imaging (MRI) may provide a non-invasive mechanism for screening aging survivors for CNS-associated neoplasms. Within the context of the St. Jude Lifetime cohort,[15] non-contrast magnetic resonance imaging of the brain was performed as a part of a broad assessment of neurocognitive status in a population of aging survivors with no previous diagnosis of a subsequent intracranial neoplasm. We report the incidental detection of intracranial neoplasms from MRI in these survivors of childhood malignancies.

Methods

Participants

The St. Jude Lifetime Cohort Study (SJLIFE) is an institutional review board-approved ongoing longitudinal study of a cohort of adult survivors of cancer diagnosed and treated at St. Jude Children's Research Hospital (SJCRH), who are ten or more years from their

original cancer diagnosis and 18 years of age at enrollment. Participation involves completion of questionnaires and a risk-based medical evaluation as recommended by the Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers developed by the Children's Oncology Group.[16] Details of eligibility, recruitment methods and study design have been previously published.[15,17]

The current study included a sample of participants from the larger SJLIFE cohort, who received non-contrast MRI as a part of a broad evaluation of neurocognitive outcomes in aging survivors. Recruitment included adult survivors of childhood HL, and ALL. Patients were excluded if they had a history of a previous genetic diagnosis with known association with neurocognitive impairment (e.g., Down syndrome), had previously been diagnosed with a secondary intracranial neoplasm, or were actively receiving anti-cancer therapy. All survivors provided informed written consent and the study was approved by the Institutional Review Board at St. Jude Children's Research Hospital.

Procedures

MRI examinations were obtained on a 3-Tesla platform and uniformly included sagittal T1, sagittal 3D T1, axial T2, and axial fluid attenuated inversion recovery (FLAIR) pulse sequences. Certain studies also included sagittal 3D T2-weighted sequences, sagittal 3D FLAIR imaging and temporal lobe coronal FLAIR pulse sequences. No intravenous contrast was administered for the MRI studies. Imaging review was performed by a board certified neuroradiologist (NS) using a systematic, protocol-driven assessment that included identification and quantification of intracranial neoplasms. The location and size of each neoplasm was recorded.

Statistical Analysis

Descriptive statistics for demographic and treatment characteristics and summary statistics for time from diagnosis by primary diagnosis and CRT exposure were generated for the study population. Comparison of demographics and treatment characteristics of survivors who developed a CNS subsequent neoplasm and those who did not were performed by using exact Chi-square tests. All the analyses were based on the first subsequent neoplasm only.

Results

For the 219 participants, the median age at diagnosis of childhood cancer was 6.8 years (range 0.5 to 19). The median time from diagnosis to the study MRI was 25.4 years (range 12 to 46). Fifty-two percent of participants were female. Of the 164 ALL survivors, 125 (76.2%) received CRT (Table 1). All HL survivors received thoracic radiotherapy without CRT. Because of the evolution of treatment with decreasing proportion of patients treated with CRT for ALL, survivors of ALL who received CRT had longer follow up time compared to those who did not receive CRT (Table 2).

By study MRI, nineteen of 219 adult survivors (8.7%) had a total of 31 incidentally detected subsequent intracranial neoplasms (Table 3). Of the 19 survivors, 13 had a single lesion, while multiple tumors were present among 6 survivors (2 with two tumors, 3 with three tumors, and 1 with five tumors). The median maximum size of the tumors detected was 1.5

cm (range 0.4 to 8.5 cm). Subsequent intracranial neoplasms were detected in 18 of 164 survivors of ALL (11%), and 1 of 55 of HL (1.8%). All but one patient with subsequent neoplasms had received CRT for their childhood malignancy. A single survivor of HL who did not have CRT had a vestibular schwannoma detected by MRI. Notably, however, this lesion occurred within a cervical radiation field that included the internal auditory canals. The prevalence of an incidentally detected subsequent neoplasm among all survivors who received CRT was 14.4% (18 of 125), and for the subset of survivors of ALL who received CRT was 14.4% (18 of 125). For survivors with a subsequent neoplasm, detailed chemotherapy and CRT exposure data are provided in Supplemental Table 1.

All survivors with a subsequent intracranial neoplasm were over 20 years from diagnosis and completion of CRT. Survivors who developed a subsequent intracranial neoplasm were more likely to have been treated with CRT (18/19, 94.7%) than survivors who did not develop a subsequent neoplasm (107/200, 53.5% treated with CRT; $p < 0.001$). Among survivors who received CRT (Table 3), survivors with a subsequent neoplasm were more likely to have received higher doses of CRT ($p = 0.01$) and had a longer time from diagnosis ($p = 0.002$) to the study MRI. All patients received chemotherapy; however, on univariate analysis no chemotherapeutic agents were associated with an increased risk of subsequent neoplasm.

On unenhanced MRI examination, 30 of the 31 neoplasms identified were predominantly solid extra-axial masses (Figure 1). Most demonstrated signal intensity that was isointense to hypointense compared with cerebral cortex on the T1-weighted images and of higher intensity than cortex on the T2-weighted and FLAIR images although some were of low signal intensity T1 and T2-weighted images, presumably due to calcification. One patient had a mixed solid and cystic mass centered in the left cerebellopontine angle (CPA) cistern that was later proven surgically to be a vestibular schwannoma. Six patients had multiple tumors. All but three subsequent neoplasms were supratentorial. Three of the survivors with subsequent neoplasms (15.8%) had tumors that involved or abutted the superior sagittal sinus (Figure 1c).

Five of the survivors with subsequent neoplasms reported general symptoms such as headache or dizziness, not definitely related to the presence of a tumor. Only one patient, who had tinnitus and a surgically proven vestibular schwannoma, had a focal symptom directly attributable to the tumor and was the only patient to report previously seeking medical attention for these symptoms. One patient with a large (5.4 cm $\times$ 4.5 cm $\times$ 4.7 cm, Figure 1a and b) meningioma in the right parietal region reported no symptoms when initially evaluated but later complained of occasional right-sided headaches and blurred vision on neurosurgical consultation.

Including the vestibular schwannoma, six patients had seven tumors resected. By histopathology, 4 of these were World Health Organization (WHO) grade 1 meningiomas, one was a WHO grade 2 atypical meningioma and one was a meningioma with unspecified grade. An additional lesion was treated with stereotactic radiosurgery without biopsy or resection. The remaining patients with identified lesions are being followed with serial imaging or declined future follow-up.

Discussion

To our knowledge, the current study represents the largest cross-sectional assessment of MRI for the incidental detection of subsequent intracranial neoplasms in long-term survivors of childhood cancer. Our findings suggest that aging survivors of childhood malignancies who received CRT are at significant risk for developing subsequent intracranial neoplasms detectable by non-contrast screening MRI. Based on their appearance, all but one of the neoplasms detected in this investigation had imaging characteristics most suggestive of a meningioma.[18] The other major radiation-related intracranial tumor, high grade glioma, is, unlike meningioma, most commonly intra-axial and usually occurs sooner after therapy.[3,19] Six of the tumors in our study were proven to be meningiomas after surgical resection. The prevalence of subsequent intracranial neoplasms after CRT (14.4% among 125 survivors at a mean of 27.8 years from therapy) in our cohort is similar to that reported in other recent studies of survivors who received CRT, such as those of Banerjee et al.[11] (22% among 49 irradiated survivors at a mean of 25 years after completion of CRT) and Goshen et al.[8] (17% among 88 irradiated survivors at a mean of 21.3 years after therapy). Those earlier studies, however, included contrast-enhanced imaging which increases the sensitivity for detection of small intracranial neoplasms, including meningiomas, and raises the possibility that the absence of contrast in our investigation may contribute to underestimation of the prevalence of subsequent neoplasms.[20]

Only one patient, who had a vestibular schwannoma, sought medical attention prior to MRI screening for a neurologic complaint (tinnitus) that was directly due to the neoplasm, suggesting that late-onset subsequent intracranial neoplasms may be amenable to detection by MRI screening before clinical symptoms prompt medical evaluation. In fact, in our study even very large subsequent neoplasms remained asymptomatic for an extended period of time. Detection of large tumors that exerted mass effect on adjacent structures or were situated near the superior sagittal sinus highlight the fact that meningiomas typically grow slowly and insidiously. Given the prevalence of subsequent neoplasms in our study participants who had received CRT, the even higher prevalence reported by other investigators[8,11], and given that the prevalence increases with length of time from primary cancer diagnosis and treatment, periodic screening of aging survivors of childhood cancer with non-contrast brain MRI may be warranted.

Other investigators have previously suggested screening for meningiomas in the long-term follow-up of children treated for malignancies with CRT based on smaller evaluated populations.[8,11,12,21] Those investigations, however, did not assess the symptomatology of those who developed subsequent intracranial neoplasms. Currently there are no evidence- or consensus-based guidelines for screening aging survivors for subsequent intracranial neoplasms, but the current study substantiates previous findings and suggests that a prospective trial is warranted to evaluate the efficacy of MRI screening.

Our investigation, however, is insufficient to reach conclusions about the advisability of screening. While MRI of the brain is the preferred imaging technique to identify intracranial tumors and establish their proximity to critical structures, its value as a screening instrument has not been systematically evaluated in survivors of childhood cancer. The financial cost of

screening, the risks and benefits associated with early detection and impact on outcomes are just some of the factors to examine when considering screening childhood cancer survivors for subsequent intracranial neoplasms.[14] While it may seem that early detection of subsequent intracranial neoplasms has the potential to improve outcomes by allowing management of tumors before they lead to transient or permanent neurological impairment or become involved with critical structures, there is no definitive data concerning such benefit. As discussed in a recent review by Bowers, et al., there is a need for prospective investigations that will assess the true risks, harms and benefits, as well as the cost associated with screening, and provide guidance regarding which survivors should be screened and at what intervals.[14]

Our investigation concurs with findings from previous studies by identifying that the detection of subsequent intracranial neoplasms was associated with increasing time from primary cancer diagnosis as well as with CRT exposure. Survivors of ALL who did not receive CRT had a shorter follow-up time compared to survivors of ALL who did receive CRT, as would be expected due to recent changes in treatment strategies. With time, these survivors may develop subsequent CNS-associated neoplasms but none were identified in this study. Stratified analysis among participants who received CRT indicates that risk for detection of subsequent neoplasms increases with time. The association between CRT exposure and subsequent development of meningiomas is well-documented in the literature. [8,10,11] Tumors are seen after a wide range of radiation doses although higher doses are associated with a greater risk for the development of a subsequent neoplasm.[4,5,7,11,22,23] Radiation-associated meningiomas are known to have a long latency period and are detected in larger numbers in those who are greater than 20 years post-CRT.[3,5,8,10,11,19,23,24] This increase over time shows no evidence of plateau.[7,11,23]

In our study, two patients, both of whom had received greater than 20 Gray of CRT for their primary tumor, received subsequent doses of CRT for relapse. It is not clear, however, to what extent the second treatments contributed to subsequent neoplasm development. Notably, we did not identify an association between chemotherapy exposure and the development of a secondary neoplasm. However, at least one previous study has identified a high incidence of secondary malignant brain tumors after CRT and antimetabolite exposure. [25]

One HL survivor in our study who did not receive CRT had a cerebellopontine angle cistern mass that was determined by histopathology to represent a vestibular schwannoma. However, the cerebellopontine angle regions and internal auditory canals for this patient, whose study MRI was performed almost 39 years after his HL diagnosis, were certainly within the radiation treatment field for the patient's childhood malignancy. Associations have been reported between childhood radiation exposure and subsequent development of vestibular schwannomas[26-29] which are associated with a long latency period.[26,28]

Limitations of this study include the absence of contrast enhanced imaging for the MRI examinations, which may limit detection of subsequent tumors, particularly small meningiomas.[20] The use of contrast may increase detection of small lesions leading to a higher prevalence of subsequent tumors in long-term survivors. Secondly this was a cross-

sectional evaluation and, thus, could not assess the cumulative incidence of subsequent neoplasms over time. Additionally, survivors with previous secondary intracranial neoplasms were not included based on the design of the parent evaluation of neurocognitive outcomes which may result in an underreporting of the actual prevalence of subsequent CNS-associated neoplasms among all survivors who received CRT as primary therapy. Also, the variability in the MRI pulse sequences used for the different imaging protocols for different participant groups in this study could conceivably affect neoplasm detection. Any potential effect, however, is likely minimal as the only group in which neoplasms were not detected are survivors who had not received CRT. Given the known association between CRT and meningiomas, the group without CRT would be expected to have few, if any neoplasms, even on longer follow-up. Finally, the small size of this study precluded the use of multivariate analyses, thus the independent nature of the relationship between CRT dose exposure and time from diagnosis cannot be ascertained.

Despite the limitations of our study, the high prevalence of incidentally detected subsequent late intracranial neoplasms after CRT and the minimal symptoms reported by study participants with intracranial tumors suggest that periodic screening of those survivors with MRI may be warranted. Screening may lead to early detection and implementation of appropriate treatment, thus giving patients the best opportunity of an optimal outcome. However, additional prospective studies are needed before any definitive recommendations for screening can be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

Unenhanced sagittal T1-weighted (a) and axial T2-weighted (b) images of the brain of a 33 year old man who had completed CRT for ALL 30.3 years prior to the MRI study demonstrate a large mass (arrows) in the right parietal lobe that was a surgically proven WHO Grade II atypical meningioma. An axial T2-weighted MR image of the brain (c) of a 49 year old woman who was treated with CRT for ALL 34 years before the study MRI reveals a 1.7 cm mass (arrow), suggestive of a meningioma, overlying the parasagittal left parietal lobe with extension into the adjacent superior sagittal sinus (arrowhead). The patient had 4 other smaller intracranial neoplasms with imaging characteristics suggestive of meningiomas.

Table 1
Demographic and treatment characteristics of survivors by primary diagnosis

	Total		Acute Lymphoblastic Leukemia		Hodgkin Lymphoma	
	N	%	N	%	N	%
	219	100	164	74.9	55	25.10%
Sex						
Male	106	48.4	81	49.4	25	45.5
Female	113	51.6	83	50.6	30	54.5
Age at primary diagnosis (years)						
0-4	89	40.6	89	54.3	0	0
5-9	43	19.6	38	23.2	5	9.1
10-14	48	21.9	31	18.9	17	30.9
15-19	39	17.8	6	3.7	33	60
Race						
Non-Hispanic White	195	89.0	146	89	49	89.1
Non-Hispanic Black	19	8.7	13	7.9	6	10.9
Hispanic	1	0.5	1	0.6	0	0
Other	4	1.8	4	2.4	0	0
Current Age (years)						
10-19	1	0.5	1	0.6	0	0
20-29	73	33.3	73	44.5	0	0
30-39	83	37.9	61	37.2	22	40
40-50	56	25.6	26	15.9	30	54.6
>=50	6	2.7	3	1.8	3	5.5
CRT (Gy)						
30	1	0.5	1	0.6	0	0
20-30	56	25.6	56	34.2	0	0
<20	68	31.1	68	41.5	0	0
None	94	42.9	39	23.8	55	100
Intracranial SNs detected	19	8.7	18	11	1	1.8

Table 2
Summary of age and time from diagnosis and from treatment with CRT by primary diagnosis and CRT exposure

	ALL		HL	All Patients
	No CRT	CRT	No CRT	
N	39	125	55	219
Age at diagnosis (years)				
Mean	10	5.1	15.3	8.5
SD	3.9	3.7	3.2	5.6
Median	9.4	3.7	16.1	6.8
Range	3.8-18.6	0.5-15.6	6.2-19.0	0.5-19.0
Time from diagnosis to study MRI (years)				
Mean	15	28.6	26.6	25.7
SD	1.8	6	5.2	7.3
Median	15	27.9	25.1	25.4
Range	12.0-17.9	19.2-46.0	18.3-39.6	12.0-46.0
Age at CRT (years)				
Mean	--	6	--	
SD	--	3.7	--	
Median	--	4.6	--	
Range	--	1.6-15.7	--	
Time from CRT to study MRI (years)				
Mean	--	27.8	--	
SD	--	6.3	--	
Median	--	27.2	--	
Range	--	17.6-45.8	--	

CRT, cranial radiation therapy; ALL, acute lymphoblastic leukemia; HL, Hodgkin lymphoma; MRI, magnetic resonance imaging

Table 3
Analyses of potential risk factors associated with the development of subsequent intracranial neoplasms

	CRT Yes		CRT No	
	Intracranial Subsequent Neoplasm N (%)	No Intracranial Subsequent Neoplasm N (%)	Intracranial Subsequent Neoplasm N (%)	No Intracranial Subsequent Neoplasm N (%)
Sex	18 (100)	107 (100)	1* (100)	93 (100)
Male	7 (38.9)	51 (47.7)	1 (100)	47 (50.5)
Female	11 (61.1)	56 (52.3)	0 (0)	46 (49.5)
Age at primary diagnosis (years)				
0-4 yrs	12 (66.7)	73 (68.2)	0 (0)	4 (4.3)
5-9 yrs	4 (22.2)	17 (15.9)	0 (0)	22 (23.7)
10-14 yrs	2 (11.1)	15 (14.0)	1	30 (32.3)
15-19 yrs	0 (0)	2 (1.9)	0 (0)	37 (39.8)
Time from Diagnosis (years)				
10-19	0 (0)	2 (1.9)	0 (0)	42 (45.2)
20-29	4 (22.2)	75 (70.1)	0 (0)	35 (37.6)
30-39	11 (61.1)	24 (22.3)	1 (100)	16 (17.2)
40-49	3 (16.7)	6 (5.6)	0 (0)	0 (0)
Race				
Non-Hispanic White	16 (88.9)	96 (89.7)	1 (100)	82 (88.2)
Others	2 (11.1)	11 (10.3)	0 (0)	11 (11.8)
CRT dose				
30 Gy	0 (0)	1 (0.93)	--	--
20-<30Gy	14 (77.8)	42 (39.3)	--	--
<20Gy	4 (22.2)	64 (59.8)	--	--

* This patient had a vestibular schwannoma that was in a cervical radiation field that included the internal auditory canals.
CRT, cranial radiation therapy; Gy, Gray