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Scientific Article

Radiation Therapy for Young Children Treated With High-Dose Chemotherapy and Autologous Stem Cell Transplant for Primary Brain Tumors

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Abstract

Purpose: : The role of peri-transplant radiation therapy (RT) in children with primary brain tumors is unclear. We characterized our institutional practice patterns and patient outcomes.

Methods and Materials: The cohort included all patients treated with high-dose chemotherapy and autologous stem cell transplant for primary brain tumors at our institution from 2011 to 2017. Rates of local control, progression-free survival, overall survival, and radiation-associated injury were assessed.

Results: Of the 37 eligible patients, 29 (78%) received peri-transplant RT. Patients treated with RT were more likely to have metastatic (P = .0121) and incompletely resected (P = .056) disease. Of those treated with RT, 13 (45%) received craniospinal irradiation (CSI) and 16 (55%) received focal RT. The median CSI dose was 23.4 Gy (interquartile range [IQR], 18-36 Gy; boost: median, 54 Gy [IQR, 53.7-55.8 Gy]) and focal RT dose was 50.4 Gy [IQR, 50.4-54.5 Gy]). Compared with the focal RT group, patients treated with CSI were older (P = .0499) and more likely to have metastatic disease (P = .0004). For the complete cohort, 2-year local control was 82% (95% confidence interval [CI], 70%-96%), progression-free survival 63% (95% CI, 49%-81%), and overall survival 65% (95% CI, 51%-82%). These rates did not differ significantly between patients treated with and without peri-transplant RT. Two cases of fatal myelopathy were observed after spinal cord doses within the highest tertile (41.4 cobalt Gy equivalent and 36 Gy).

Conclusions: Peri-transplant RT was used for high-risk disease. Oncologic outcomes after RT were encouraging. However, 2 cases of grade 5 myelopathy were observed. If used cautiously, RT may contribute to durable remission in patients at high risk of relapse.

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Introduction

The management of brain tumors in infants and very young children is challenging. In older children, radiation therapy (RT) is often a part of the standard management and contributes to favorable oncologic outcomes. However, in young children, RT, particularly craniospinal irradiation (CSI), can cause profound late neurocognitive effects.[1-4] Therefore, high-dose chemotherapy (HDC) with autologous stem cell transplant (ASCT) is used to delay or avoid RT in this patient population. The cooperative group studies Children's Cancer Group (CCG)−99703 and ACNS0334 explored the use of HDC/ASCT in young children with newly diagnosed malignant brain tumors.[5,6] Neither trial included RT as a part of the study design; instead, both left the use of RT to the discretion of the treating physician and the patient's family. Thus, the role of RT in this setting is unclear.

Historically, at our institution, we have used peri-transplant RT for brain tumors in young children whom we considered to be at a high risk of disease relapse. We have treated select patients with CSI or focal irradiation of the tumor and/or resection cavity. In this work, we aimed to: (1) characterize our use of RT for pediatric brain tumors treated with HDC/ASCT; (2) assess local control (LC), progression-free survival (PFS), and overall survival (OS) in patients who did and who did not receive peri-transplant RT; and (3) evaluate for radiation-associated injury in patients treated with peri-transplant RT.

Methods and Materials

This retrospective cohort study included all patients treated at our institution with HDC/ASCT for primary brain tumors from January 2011 to July 2017. After institutional review board approval was obtained, patient, disease, and outcome data were extracted from the electronic medical record. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Outcomes of interest

Oncologic outcomes included LC, defined as freedom from relapse within 1 cm of the initial site of gross disease or the postoperative tumor bed; PFS, defined as freedom from relapse or death of any cause; and OS. In addition, we assessed the incidence of radiation-associated injury among patients treated with peri-transplant RT. Given the study design, we were unable to assess for late treatment-related toxic effects, such as neurocognitive outcomes.

Statistical analyses

Variables were summarized using frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables. Patient characteristics were compared using χ^2, Fisher exact, or Wilcoxon rank sum tests.

Times to local progression, any progression, and death were defined as the time from the posttherapy magnetic resonance imaging (MRI) scan until the event of interest. The posttherapy MRI scan was typically performed 4 to 6 weeks after the completion of therapy (ie, after HDC/ASCT or RT, whichever was given later). We used this time point so follow-up times would not be influenced by the treatment sequence. If no event occurred, patients were censored at the date of last follow-up or death. Kaplan-Meier curves were created for time to each event. Log-rank statistics were used to test for differences in time-to-event by patient groups. R version 4.0.2 R software (R Foundation for Statistical Computing) was used for statistical analyses, and the significance level was set at 0.05. All tests were 2-sided.

Results

Patient characteristics

A total of 37 patients were treated with HDC/ASCT for primary central nervous system (CNS) tumors during the study period. Of these, 29 (78%) received peri-transplant RT. Characteristics of patients who did versus did not receive peri-transplant RT are compared in Table 1. In patients who were not selected for RT (n = 8), the most common histology was medulloblastoma (75%); the molecular subgroup was sonic hedgehog in 5 (83%) and group 3 in 1 (17%). Conversely, in patients who were treated with peri-transplant RT, most patients had tumor histologies other than medulloblastoma (59% had atypical teratoid rhabdoid tumor [ATRT], nongerminomatous germ cell tumor, pineoblastoma, primitive neuroectodermal tumor [PNET], or glioneuronal tumor; P = .12 for medulloblastoma vs other histology). Of the 12 patients with medulloblastoma who received RT, molecular subgrouping was possible for 10; it was group 3 in 6 (50%), group 4 in 1 (8%), sonic hedgehog in 2 (17%), and not otherwise specified (NOS) in 1 (8%). Most patients (52%) treated with peri-transplant RT had metastatic disease, whereas all patients treated without RT had localized disease (P = .01). Fewer patients treated with RT had

Table 1 Characteristics of patients treated with peri-transplant radiation versus those treated without peri-transplant radiation

Characteristic	Peri-transplant RT (n = 29)	No peri-transplant RT (n = 8)	*P* value
Sex, n (%)			.431
Female	13 (45)	2 (25)	
Male	16 (55)	6 (75)	
Age at diagnosis (y), median (IQR)	3.8 (1.5-7.3)	2.4 (1.6-2.9)	.2994
Diagnosis, n (%)			.5735
ATRT	5 (17)	0 (0)	
Glioneuronal tumor	1 (3)	0 (0)	
Medulloblastoma	12 (41)	6 (75)	
SHH	2 (17)	5 (83)	
WNT	0 (0)	0 (0)	
Group 3	6 (50)	1 (17)	
Group 4	1 (8)	0 (0)	
NOS	1 (8)	0 (0)	
Unknown	2 (17)	0 (0)	
NGGCT	2 (7)	1 (12)	
Pineoblastoma	1 (3)	0 (0)	
PNET	8 (28)	1 (12)	
Medulloblastoma, n (%)			.1245
No	17 (59)	2 (25)	
Yes	12 (41)	6 (75)	
Extent of disease at presentation, n (%)			.0121
Local	14 (48)	8 (100)	
Metastatic	15 (52)	0 (0)	
Site of primary tumor, n (%)			1
Diffuse LMD	3 (10)	0 (0)	
Supratentorial	7 (24)	2 (25)	
Infratentorial	18 (62)	6 (75)	
Spinal cord	1 (3)	0 (0)	
Extent of resection, n (%)			.056
GTR/NTR	9 (31)	6 (75)	
STR	15 (52)	1 (12)	
Unknown	5 (17)	1 (12)	
Timing of HDC/ASCT, n (%)			1
Frontline	21 (72)	6 (75)	
Salvage	8 (28)	2 (25)	
HDC regimen, n (%)			.492
ACNS0333	5 (17)	1 (12)	
ACNS0334 or similar	12 (41)	6 (75)	
CCG99702	6 (21)	0 (0)	
Other	6 (21)	1 (12)	

(*continued on next page*)

Table 1 (*Continued*)

Characteristic	Peri-transplant RT (n = 29)	No peri-transplant RT (n = 8)	*P* value
Number of ASCTs, n (%)			.75
1	5 (17)	2 (25)	
2	8 (28)	1 (12)	
3	16 (55)	5 (62)	
Methotrexate, n (%)			.1598
No	21 (72)	8 (100)	
Yes	8 (28)	0 (0)	

Abbreviations: ASCT = autologous stem cell transplant; ATRT = atypical teratoid rhabdoid tumor; CCG = Children's Cancer Group; GTR = gross total resection; HDC = high-dose chemotherapy; IQR = interquartile range; LMD = leptomeningeal disease; NGGCT = nongerminomatous germ cell tumor; NOS = not otherwise specified; NTR = near total resection; PNET = primitive neuroectodermal tumor; RT = radiation therapy; SHH = sonic hedgehog; STR = subtotal resection.

undergone a gross or near total resection (GTR/NTR; 31% vs 75%, $P = .056$). Those treated with peri-transplant RT were older; however, this difference was not statistically significant (median, 3.8 years [IQR, 1.5-7.3 years] vs 2.4 years [IQR, 1.6-2.9 years], $P = .3$). There was no difference between the 2 groups with respect to sex, site of primary tumor, timing of HDC/ASCT (ie, frontline vs salvage), HDC regimen, number of ASCTs, or use of methotrexate.

We repeated these analyses excluding patients with ATRT because the management of ATRT typically involves HDC/ASCT and RT, as was done on the ACNS0333 study.[7] In other words, peri-transplant RT is recommended for patients with ATRT regardless of other clinical features. Therefore, we explored the characteristics of patients who were selected for RT to treat any tumor type other than ATRT. In this subset (n = 32), findings were similar as for the overall cohort. Most patients (58%) treated with RT had metastatic disease, and all patients (100%) treated without RT had localized disease ($P = .004$). Fewer patients treated with RT had undergone a GTR/NTR (29% vs 75%, $P = .09$). Those treated with peri-transplant RT were older (median, 4.1 years [IQR, 2.4-8.5 years] vs 2.4 years [IQR, 1.6-2.9 years], $P = .08$). There was no difference between the 2 groups with respect to sex, histology, site of primary tumor, timing of HDC/ASCT (ie, frontline vs salvage), HDC regimen, number of ASCTs, or use of methotrexate.

Peri-transplant radiation details

Of the 29 patients treated with peri-transplant RT, 13 (45%) received CSI and 16 (55%) received focal RT. All patient received photon therapy, with the exception of one patient treated with focal RT who received proton therapy. The median CSI dose was 23.4 Gy (IQR, 18-36 Gy). Eleven patients received a boost after CSI to give a total median dose to the tumor of 54 Gy (IQR, 53.7-55.8 Gy). Two patients treated with CSI did not receive a boost because there was no obvious primary tumor. CSI and the boost were given before HDC/ASCT in 6 patients and after HDC/ASCT in 5 patients; in 2 patients, CSI was given before HDC/ASCT and the boost given afterward. Of the 16 patients treated with focal RT, 12 received conventionally fractionated RT to a median dose of 50.4 Gy (IQR, 50.4-54.5 Gy). The remaining 4 patients received hypofractionated stereotactic radiosurgery (SRS, 25 Gy in 5 fractions, n = 2; 24 Gy in 3 fractions, n = 2). Focal RT was given before HDC/ASCT in 10 patients, after HDC/ASCT in 5 patients, and in between cycles of HDC/ASCT in 1 patient.

Characteristics of patients treated with CSI and focal RT are summarized in Table 2. Patients who received CSI were significantly older at the time of RT (median, 6.2 years [IQR, 3.9-10.3 years] vs 2.6 years [IQR, 1.5-5.2 years], $P = .0499$). Those who received CSI were more likely to have had metastatic disease (92% vs 19%, $P = .0004$). The only patient treated with CSI who did not have metastatic disease upfront was an 8-year-old boy with a pineal nongerminomatous germ cell tumor. His beta-HCG did not normalize after 6 cycles of chemotherapy on ACNS1123 stratum 1, and he was removed from the study and underwent HDC/ASCT followed by CSI. When comparing patients treated with CSI versus focal RT, there was no difference in diagnosis, site of the primary tumor, extent of resection, timing of HDC/ASCT (frontline vs salvage), HDC regimen, number of ASCTs, or radiation modality.

Oncologic outcomes

The median follow-up time for the whole cohort was 3.8 years (IQR, 0.9-6.3 years). The 2-year probability of LC was 82% (95% CI, 70%-96%), PFS was 63% (95% CI,

Table 2 Characteristics of patients treated with focal radiation therapy versus those treated with craniospinal irradiation

Characteristic	Focal RT (n = 16)	CSI (n = 13)	*P* value
Age at RT (y), median (IQR)	2.6 (1.5-5.2)	6.2 (3.9-10.3)	.0499
Diagnosis, n (%)			.286
ATRT	4 (25)	1 (8)	
Glioneuronal tumor	1 (6)	0 (0)	
Medulloblastoma	5 (31)	7 (54)	
NGGCT	0 (0)	2 (15)	
Pineoblastoma	1 (6)	0 (0)	
PNET	5 (31)	3 (23)	
Medulloblastoma, n (%)			.3955
No	11 (69)	6 (46)	
Yes	5 (31)	7 (54)	
Extent of disease at presentation, n (%)			.0004
Local	13 (81)	1 (8)	
Metastatic	3 (19)	12 (92)	
Site of primary tumor, n (%)			.9248
Diffuse LMD	1 (6)	2 (15)	
Supratentorial	4 (25)	3 (23)	
Infratentorial	10 (62)	8 (62)	
Spinal cord	1 (6)	0 (0)	
Extent of resection, n (%)			1
GTR/NTR	5 (31)	4 (31)	
STR	8 (50)	7 (54)	
Unknown	3 (19)	2 (15)	
Timing of HDC/ASCT, n (%)			.2378
Frontline	10 (62)	11 (85)	
Salvage	6 (38)	2 (15)	
HDC regimen, n (%)			.1685
ACNS0333	4 (25)	1 (8)	
ACNS0334 or similar	8 (50)	4 (31)	
CCG99702	1 (6)	5 (38)	
Other	3 (19)	3 (23)	
Number of ASCTs, n (%)			.4132
1	4 (25)	1 (8)	
2	3 (19)	5 (38)	
3	9 (56)	7 (54)	
Radiation modality, n (%)			1.0
Photon	15 (94%)	13 (100%)	
Proton	1 (6%)	0	

Abbreviations: ASCT = autologous stem cell transplant; ATRT = atypical teratoid rhabdoid tumor; CCG = Children's Cancer Group; CSI = craniospinal irradiation; GTR = gross total resection; HDC = high-dose chemotherapy; IQR = interquartile range; LMD = leptomeningeal disease; NGGCT = nongerminomatous germ cell tumor; NTR = near total resection; PNET = primitive neuroectodermal tumor; RT = radiation therapy; STR = subtotal resection.

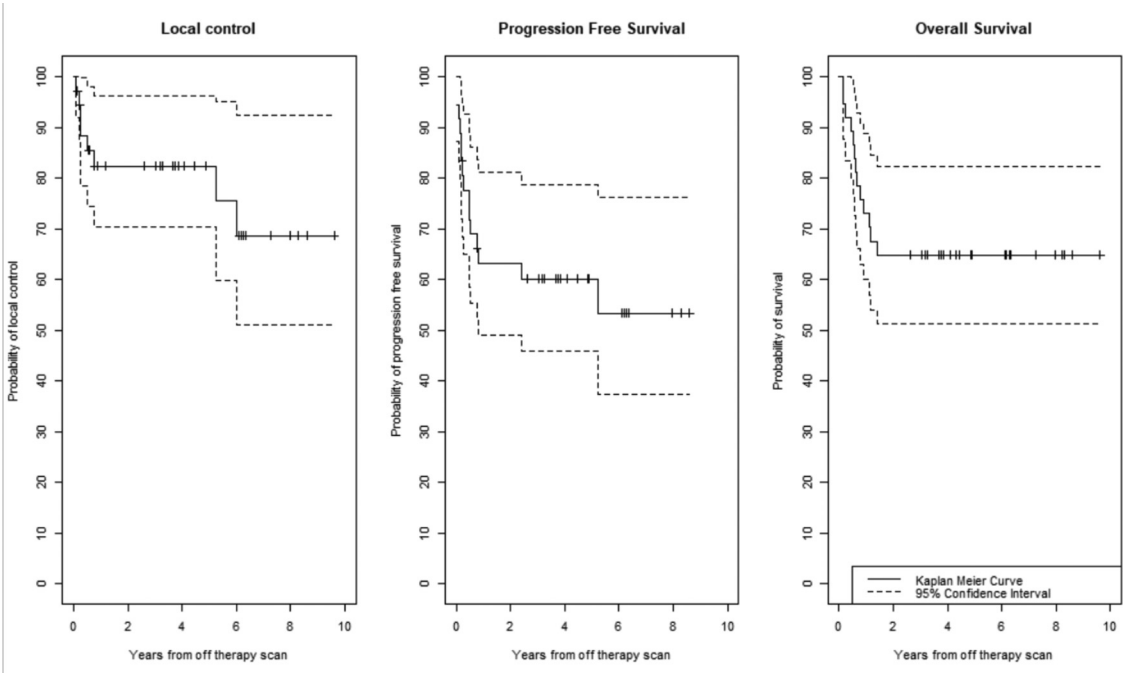

Figure 1 Local control, progression-free survival, and overall survival for the complete cohort.

49%-81%), and OS was 65% (95% CI, 51%-82%) for the complete cohort (Fig. 1).

The subgroup of 29 patients who were treated with peri-transplant RT had a median follow-up time of 3.2 years (IQR, 0.7-6.1 years). During this time, a total of 5 local relapses, 12 relapses (local or distant), and 12 deaths were observed. Of the 5 local (in-field) recurrences, 1 was proven pathologically and the other 4 received a diagnosis based on clinical and radiographic findings. For this group, the 2-year probability of LC was 85% (95% CI, 72%-100%), of PFS was 60% (95% CI, 44%-81%), and of OS was 59% (95% CI, 43%-80%).

The 8 patients who did not receive peri-transplant RT were followed for a median of 5.3 years (IQR, 3.7-7.4 years). During this time, a total of 3 local relapses, 3 relapses (local or distant), and 1 death were observed. In all 3 patients who experienced disease relapse, the first site of relapse was local. The diagnosis of local recurrence was made based on a biopsy in one case, on radiographic findings in the setting of increasing tumor markers in the second case, and on radiographic and clinical findings in the third case. The 2-year probability of LC and PFS was 75% (95% CI, 50%-100%) and of OS was 88% (95% CI, 67%-100%).

When comparing patients treated with or without peri-transplant RT, we did not identify a statistically significant difference in LC, PFS, or OS (Fig. 2A). OS rates were non-significantly lower in those patients treated with peri-transplant RT. Similarly, when comparing patients across the 3 strata of peri-transplant focal RT, peri-transplant CSI, or no peri-transplant RT, there was no statistically significant difference in LC, PFS, or OS (Fig. 2B). Although the difference did not reach statistical significance (P = .11), the highest OS rate was seen in those patients who were not selected for peri-transplant RT, followed by those treated with peri-transplant CSI, followed by those treated with peri-transplant focal RT.

Similarly, when the subset of patients treated with RT was stratified by localized versus metastatic disease, no difference in oncologic outcomes was observed. Among patients treated with RT who had localized versus metastatic disease, respectively, 2-year LC was 76% (95% CI, 55%-100%) versus 93% (95% CI, 82%-100%), PFS was 68% (95% CI, 46%-100%) versus 53% (95% CI, 32%-86%), and OS was 57% (95% CI, 36%-90%) versus 60% (95% CI, 40%-91%).

Toxic effects

In our cohort, 3 patients developed grade 3 to 5 radiation injury. The first case was observed in a boy with multiply recurrent medulloblastoma. His initial therapy included 23.4 Gy CSI and a boost to the posterior fossa for a total of 55.8 Gy, with concurrent carboplatin and vincristine and adjuvant cisplatin, vincristine, and lomustine (CCNU). His disease recurred 3 years later. He was treated with HDC comprising carboplatin, thiotepa, and etoposide. One month after his ASCT, an MRI revealed 2 new brain metastases: one in the left frontal lobe, and the other in the left cerebellum. Both metastases were treated with fractionated SRS to a total dose of 24 Gy in 3

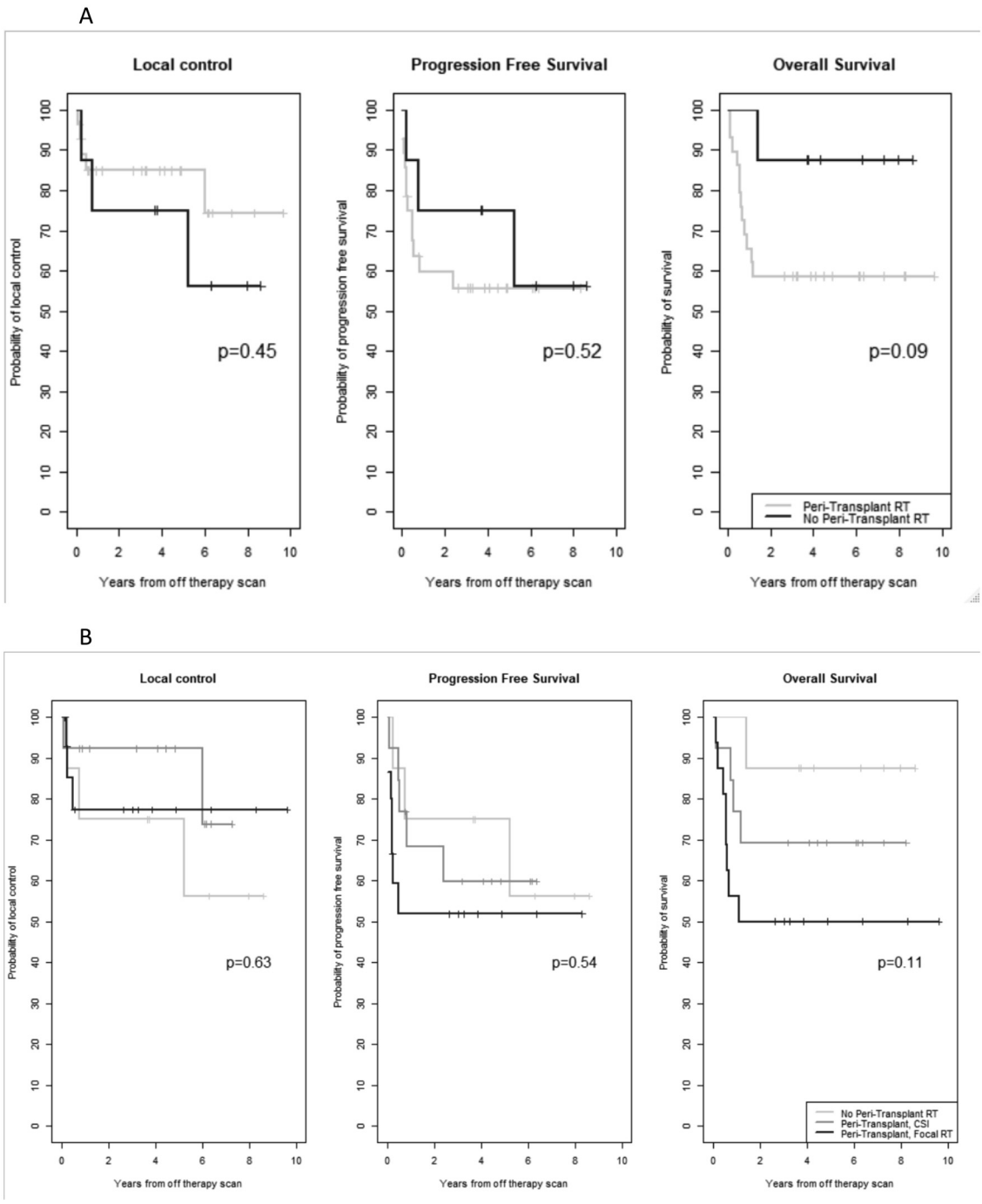

Figure 2 Local control, progression-free survival, and overall survival. (A) Patients stratified by peri-transplant radiation versus no peri-transplant radiation. (B) Patients stratified by peri-transplant focal radiation versus peri-transplant craniospinal irradiation versus no peri-transplant radiation. *Abbreviations:* CSI = craniospinal irradiation; RT = radiation therapy.

fractions. All RT in this case was given with photons. Three months after SRS, he developed acute ataxia. He was diagnosed with radiation necrosis within the area that had received 55.8 Gy remotely, followed more recently by fractionated SRS. The patient was treated with bevacizumab and dexamethasone, with resolution of his symptoms. At his most recent follow-up, 10 years after ASCT, the patient was alive and without evidence of disease.

The other 2 cases of radiation injury involved grade 5 myelopathy. The first patient was a girl with localized ATRT of the cervicomedullary junction who received a diagnosis when she was 6 months old. She was treated with induction methotrexate, vincristine, etoposide, cyclophosphamide, and cisplatin according to ACNS0333. Then, she received focal proton therapy to a total of 41.4 cobalt Gy equivalent (CGE), followed by an additional 9

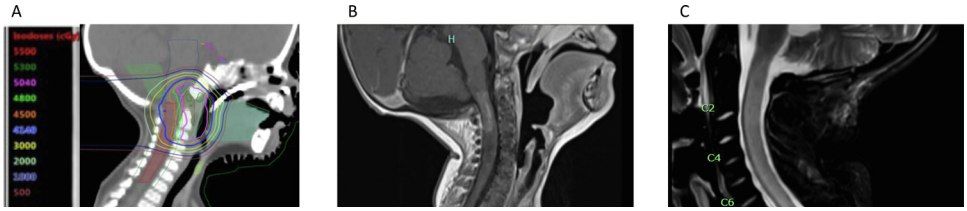

Figure 3 Sagittal images for the 2 cases of grade 5 myelopathy. (A) Focal radiation plan for the first patient (fuschia = 5040 cGy isodose line; blue = 4140 cGy isodose line). (B) T1 gadolinium-enhanced magnetic resonance imaging for the first patient demonstrating patchy enhancement extending from the medulla to the level of C5. (C) T2 magnetic resonance imaging for the second patient, who had been treated with craniospinal irradiation, showing T2 signal abnormality throughout the spinal cord.

CGE to the site of disease excluding the spinal cord (Fig. 3A). Then, she underwent 3 tandem ASCTs with carboplatin and thiotepa. Subsequently, she developed progressive cervical spinal cord myelopathy, with MRI scans demonstrating signal abnormality extending from the medulla into the cervical spinal cord to the level of C5 (Fig. 3B). She was treated with steroids, bevacizumab, and aggressive supportive measures; however, she died of spinal cord injury approximately 1.5 years after the completion of RT. An autopsy confirmed necrosis of the medullary olives and cervical spinal cord with no gross or microscopic tumor identified.

The second case of grade 5 myelopathy occurred in a girl with metastatic medulloblastoma with *MYC* amplification who received a diagnosis when she was 10 years old. She underwent GTR, then was treated with induction cyclophosphamide, followed by 36 Gy photon CSI with concurrent carboplatin, then 3 tandem ASCTs per CCG99702. She developed progressive spinal cord injury, with abnormal T2 signal extending throughout the spinal cord (Fig. 3C). Cerebrospinal fluid showed no evidence of infection or malignant cells. Despite treatment with steroids, bevacizumab, and aggressive supportive measures, she died approximately 1 year after the completion of CSI. No autopsy was performed but radiation myelopathy was the presumed cause of death, based on clinical and radiographic findings, as well as cerebrospinal fluid studies that excluded other diagnoses.

We explored factors associated with the risk of grade 5 myelopathy in this cohort. In total, 14 patients received spinal cord irradiation. Thirteen were treated with CSI and one with focal RT to a cervicomedullary primary tumor. These patients were divided into tertiles based on the dose to the spinal cord. Both patients who developed grade 5 spinal cord injury were in the highest dose tertile (Table 3). In this subgroup that received 36 to 41.4 Gy to the spinal cord (n = 6), grade 5 myelopathy was observed in 2 patients (33%). No case of grade 5 spinal cord injury was observed in patients treated with lower doses (ie, ≤23.4 Gy). Fatal myelopathy was observed in 2 of the 7 patients who received spinal RT before HDC/ASCT (29%); conversely, no similar case was observed in patients who received spinal RT after HDC/ASCT. Grade 5 myelopathy occurred in 1 of 3 patients (33%) who had received methotrexate and in 1 of 11 patients (9%) who had not received methotrexate. Only 1 patient in this cohort was treated with proton therapy, limiting analyses to explore the association between radiation modality and myelopathy.

Discussion

The management of brain tumors in young children is challenging. Historically, very young children with malignant brain tumors have experienced poor survival. In addition, they have experienced a high rate of treatment-related late effects, such as neurocognitive decline. RT is an important modality that contributes to cure in older children, but it is a major cause of neurotoxicity in infants and young children. These patients' poor prognoses and high risk of RT-related side effects prompted the development of regimens that use HDC/ASCT upfront, so RT can be delayed or avoided. These regimens aimed to improve oncologic outcomes and reduce treatment-related toxic effects. Trials of HDC/ASCT left the use of RT up to the physician and family, so the role of RT in this setting is unclear. In this study, we explored our

Table 3 Association of grade 5 myelopathy with spinal cord dose

Characteristic	Lowest tertile: 12-18 Gy (n = 5)	Middle tertile: 23.4 Gy (n = 3)	Highest tertile: 36-41.4 Gy (n = 6)
Grade 5 myelopathy, n (%)	0 (0)	0 (0)	2 (33)

institutional practice and patients' oncologic and toxic outcomes.

In characterizing our practice patterns, we found that RT was used preferentially for patients with a higher risk of disease relapse and a lower risk of treatment-related toxic effects. Specifically, RT was used preferentially for patients with metastatic and incompletely resected disease and with higher risk histologies. In addition, RT was used preferentially for older children, who had a lower risk of treatment-related toxic effects. By selecting patients with a higher risk of disease relapse and a lower risk of treatment-related toxic effects, we aimed to maximize the therapeutic ratio of RT.

These differences between cohorts must be borne in mind when comparing patient outcomes. As stated previously, patients who were treated with RT had higher risk disease features. For example, the majority of patients who received RT had metastatic disease, whereas all patients who did not receive RT had localized disease. Thus, the comparison of oncologic outcomes for patients treated with versus without peri-transplant RT was greatly affected by selection bias. The nonsignificantly superior PFS and OS observed in patients who did not receive RT is likely due to their lower risk disease characteristics. One limitation of our study was the small sample size that prevented us from fitting multivariable models that would account for these differences in cohort characteristics.

Oncologic outcomes were encouraging in patients treated with peri-transplant RT. As described previously, this cohort of patients had high-risk disease. Specifically, they had primarily group 3 medulloblastoma, PNET, or ATRT, over half had metastatic disease, and only a minority underwent GTR/NTR. Despite these adverse features, the 2-year rate of LC was 85%, of PFS was 60% and of OS was 59% in patients treated with peri-transplant RT. These relatively favorable oncologic outcomes suggest that peri-transplant RT may contribute to effective disease control. Furthermore, in our cohort, the 2-year mean rate of LC was slightly higher in patients treated with RT versus without RT. Also, among patients selected for RT, those treated with comprehensive CSI experienced a slightly higher 2-year mean PFS than those treated with focal RT, despite having higher risk disease features. These findings support the hypothesis that RT may improve tumor control in the peri-transplant setting. However, due to the nonrandomized study design and nonsignificant findings, additional research is needed to confirm these results in larger patient cohorts.

RT did come with a risk of toxic effects. In our cohort, there were 2 cases of fatal myelopathy. The instances of grade 5 myelopathy were observed after 41.4 CGE and 36 Gy, doses that are typically considered safe for the spinal cord. These findings are consistent with other data suggesting that that CNS-active chemotherapy reduces spinal cord tolerance.[8-12] Therefore, great care must be taken when irradiating the spinal cord in this setting. Reduction of radiation dose to the spinal cord should be considered. Furthermore, it is possible that particular caution is necessary when treating with proton therapy, given the radiobiological and dosimetric uncertainties inherent to particle therapy. In our cohort, only 1 patient was treated with proton therapy; she was 1 of the 2 patients to experience fatal myelopathy. Additional research is needed to explore the risk of toxic effects as a function of radiation modality in this setting.

Notably, both instances of fatal myelopathy occurred in patients who received RT before HDC/ASCT. Similarly, on ACNS0333, 2 deaths from CNS necrosis occurred in patients treated with RT before HDC/ASCT.[7] Deaths from CNS necrosis or myelitis were not observed in any patient who received RT after the completion of HDC/ASCT in our study or in the ACNS0333 cohort.[7] Taken together, these findings suggest that RT should be given after HDC/ASCT in this patient population.

We acknowledge the limitations of this study. One important weakness is incomplete information regarding late neurocognitive functioning of survivors. Concern about neurotoxicity leads some clinicians and families to avoid the use of RT altogether in young children, even if it results in superior tumor control. However, disease progression and salvage therapies also have detrimental effects on cognitive function and quality of life. Therefore, in patients with a high risk of disease recurrence, relapse itself may be the primary threat not only to survival, but also to good quality of life and neurocognitive function. Careful neurocognitive assessments after various upfront and salvage therapies are critical to help guide appropriate selection of therapy. In our cohort, the median follow-up time was too short to adequately assess for late toxic effects. Furthermore, effects such as neurocognitive decline are difficult to compare accurately between groups outside the confines of a clinical trial. A second limitation of this study, as stated previously, was the small and heterogeneous patient cohort. Although the cohort was large for a single institution experience and rare conditions, it was insufficient for statistical analyses that would be of interest, such as outcomes for disease subgroups in medulloblastoma or ATRT.

Conclusion

In young children treated with HDC/ASCT for primary brain tumors, the optimal role of RT remains to be defined. We identified encouraging disease control and survival rates when RT was used in the peri-transplant period for a cohort of patients at high risk of disease recurrence. Cases of grade 5 myelopathy highlight the importance of using caution when combining RT with CNS-active chemotherapy. However, if used at lower doses, RT may contribute to durable remission. This strategy deserves consideration when planning future

trials. Careful collection of radiation treatment information, oncologic outcomes, and late effects of therapy will help to define the patients for whom peri-transplant RT should be considered. In addition, the efficacy and toxicity of salvage regimens require further investigation because this information must be considered when weighing the risks and benefits of peri-transplant RT for each patient. Studies capturing these data will assist clinicians in appropriately selecting patients for RT to maximize cure rates while minimizing treatment-related toxic effects.

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