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NECROSIS AFTER CRANIOSPINAL IRRADIATION: RESULTS FROM A PROSPECTIVE SERIES OF CHILDREN WITH CNS EMBRYONAL TUMORS

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Abstract

PURPOSE—Necrosis of the CNS is a known complication of craniospinal irradiation (CSI) in children with medulloblastoma and similar tumors. We reviewed the incidence of necrosis in our prospective treatment series.

METHODS AND MATERIALS—Between 1996 and 2009, 236 children with medulloblastoma (n = 185) or other CNS embryonal tumors (n=51) received post-operative CSI followed by dose-intense cyclophosphamide, vincristine, and cisplatin. Average-risk cases (n = 148) received 23.4 Gy CSI, 36 Gy posterior fossa, and 55.8 Gy primary; after 2003, the treatment was 23.4 Gy CSI and 55.8 Gy primary. All high-risk cases (n = 88) received 36–39.6 Gy CSI and 55.8 Gy primary. The primary site clinical target volume margin was 2-cm (pre-2003) or 1-cm (post-2003). With competing risk of death by any cause, we determined the cumulative incidence of necrosis.

RESULTS—With a median follow-up of 52 months (range, 4–163 months), eight cases of necrosis were documented. One death was attributed. The median time to the imaging evidence was 4.8 months and symptoms 6.0 months. The cumulative incidence at 5 years was $3.7\% \pm 1.3\%$ (n = 236) for the entire cohort, and $4.4\% \pm 1.5\%$ (n = 196) for infratentorial tumor location. The mean relative volume of infratentorial brain receiving high-dose irradiation was significantly greater for patients with necrosis compared to those without: 50 Gy ($92.12\% \pm 4.58$ vs. $72.89\% \pm 1.96$, p = 0.0337), 52 Gy ($88.95\% \pm 5.50$ vs. $69.16\% \pm 1.97$, p = 0.0275), and 54 Gy ($82.28\% \pm 7.06$ vs. $63.37\% \pm 1.96$, p = 0.0488).

CONCLUSIONS—Necrosis in patients with CNS embryonal tumors is uncommon. When competing risks are considered, the incidence is 3.7% at 5 years. The volume of infratentorial brain receiving greater than 50, 52, and 54 Gy is predictive for necrosis.

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CONFLICT OF INTEREST NOTIFICATION PAGE

There are no conflicts of interest with the authors or materials in this manuscript.

Keywords

necrosis; medulloblastoma; craniospinal irradiation; pediatrics

Introduction

Treatment regimens for patients with CNS embryonal tumors, including medulloblastoma, are designed to achieve a high rate of disease control using craniospinal irradiation (CSI) in combination with surgery and chemotherapy. Multimodality therapy for medulloblastoma results in 5-year event free survival (EFS) rates of 79–83% for average-risk disease (1, 2) and 54–70% for high-risk disease (1, 3). Patients with other CNS embryonal tumors generally fare less well, (4, 5) although recent reports indicate that selected patients with supratentorial primitive neuroectodermal tumors (S-PNET) and atypical teratoid rhabdoid tumors (AT/RT) have 75% 5 year and 78% 3 year EFS rates, respectively. Cognitive deficits (6), endocrinopathy (7), and hearing loss (8) are common among these patients and remain primary concerns after CSI. There is limited information about the less common but potentially devastating complications including brain and spinal cord necrosis, cerebral vasculopathy, and secondary malignancies. Necrosis is a rare complication of irradiation in patients with brain and spinal cord tumors. In one review, the incidence using daily fractions of 2 Gy was predicted to be 5% when delivering a total of 72 Gy (range 60–84 Gy) and 10% for 90 Gy (range 84–102 Gy) (9). Another review suggested that the risk of injury and necrosis of the brainstem should be low when the entire brainstem is irradiated to 54 Gy or when a small portion (1–10 mL) receives up to 59 Gy using conventional fractionation (10). Because these data are derived from adult patients with head and neck tumors, low- and high-grade glioma, and brain metastases (9, 10), the incidence of necrosis for pediatric patients treated with CSI and chemotherapy remains unknown.

We reviewed the medical records, neuroimaging and toxicity reports of patients with medulloblastoma and similarly treated CNS embryonal tumors to determine the incidence of radiation-induced necrosis. Our goal was to estimate the critical combination of radiation dose and irradiated volume that might lead to necrosis in this group of patients treated prospectively with aggressive surgery and high-dose chemotherapy.

Patients and Methods

Patients

Between 1996 and 2009, 236 children (88 girls, 148 boys) with newly diagnosed CNS embryonal tumors were prospectively treated according to one of two protocols, SJMB96 (1) or SJMB03 (clinicaltrials.gov, NCT00085202), at St. Jude Children's Research Hospital. Treatment included maximum resection followed by risk-adapted, postoperative CSI and chemotherapy. This project was performed with IRB approval.

Patients ages 3 to 21 at the time of diagnosis with average-risk or high-risk disease were eligible. Average-risk patients had no evidence of metastatic disease and residual primary site disease $\leq 1.5 \text{ cm}^2$ on postoperative MRI. High-risk patients had primary site residual disease measuring $> 1.5 \text{ cm}^2$ by MRI or metastatic disease as determined by cytologic evaluation of CSF or MRI evaluation of the brain or spine. CSI was scheduled to begin within 28–31 days after surgical resection.

Treatment

Radiation Therapy—Until 2003, average-risk patients ($n = 148$) received CSI (23.4 Gy), posterior fossa irradiation (36 Gy), and primary site irradiation (55.8 Gy) using a 2-cm clinical target volume (CTV) margin. After 2003, average-risk patients received CSI (23.4 Gy) and primary site irradiation (55.8 Gy) using a 1-cm CTV. High-risk patients ($n = 88$) received CSI (36–39.6 Gy) followed by primary site irradiation (55.8 Gy) using a 2-cm (pre-2003) or 1-cm (post-2003) CTV margin. Both protocols allowed for 59.4 Gy to selected patients with substantial residual tumor; 17 patients received a prescription dose > 55.8 Gy including 3 patients with pineal region tumors.

The CSI volume included the entire subarachnoid space. When the posterior fossa was irradiated to 36 Gy after 23.4 Gy CSI, the CTV was the anatomic posterior fossa. In all cases, the gross tumor volume (GTV) for the primary site component “boost” of therapy was defined by all gross residual tumor or by the tumor bed contoured anatomically according to the tissues involved on preoperative imaging and then shaped according to postoperative imaging. The CTV margin for the primary site boost was anatomically confined. A 3-dimensional margin of 3 to 5 mm was added to the CTV to create the planning target volume (PTV). Guidelines required that 100% of the PTV receive at least 95% of the prescription dose and that no more than 10% of the PTV could receive more than 110% of the prescription dose. Posterior fossa and primary site irradiation was delivered using 3-D conformal or intensity-modulated radiation therapy methods.

Chemotherapy and Follow-Up—Chemotherapy was initiated 6 weeks after completion of radiation therapy. Patients received four cycles of high-dose cisplatin, vincristine, and cyclophosphamide. Each 4-week cycle was followed by autologous stem-cell rescue. Exactly 119 of 129 patients who received surgery and radiotherapy completed all 4 cycles of chemotherapy. The disease control outcomes for this study have not been reported.

The details of the chemotherapy regimen have been described elsewhere (1). After completion of all therapy, patients were evaluated with brain MRI every 3 months for at least the first 18 months and then every 6 months for 5 years, and annually thereafter. The schedule for spine MRI and lumbar puncture for CSF was determined by risk group.

Data Collection and Necrosis Definition

Medical records, including neuroimaging and toxicity reports were reviewed to determine the cumulative incidence of CNS necrosis. Necrosis was defined by late enhancement of normal tissues as assessed by contrast-enhanced T1-weighted MR imaging, increased signal on T2 and FLAIR imaging, and the imaging parameters of apparent diffusion coefficient, fractional anisotropy, FDG-PET, and MR spectroscopy, when available. Composite treatment plans were available for all patients and included detailed dose-volume data for normal tissue structures, including spinal cord, brainstem, cerebellum, and cerebrum. Mean dose, integrated dose, and maximum dose to specific normal tissue volumes, including spinal cord, brainstem, cerebellum, cerebrum, and infratentorial brain were calculated.

Statistical Analysis

The incidence of necrosis was calculated from the start date of radiation therapy with death considered a competing event. Patients were censored at the date of death or last follow-up. The cumulative incidence of brain necrosis was determined for the entire cohort, infratentorial tumor location, and by cranial dose level. Comparisons were made using the log-rank technique. The Wilcoxon test was used to evaluate the absolute and relative volumes of brain, brainstem, spinal cord, and infratentorial brain receiving radiation doses 50 Gy and up to 60 Gy in patients with and without necrosis. Logistic regression was used to

explore the predictors for the incidence of necrosis. The 5-year overall survival was estimated using the Kaplan-Meier method.

Results

Clinical characteristics of patients are presented in Table 1. The surviving patients were followed for a median of 52 months (range, 4–163 months). Eight cases of brain necrosis were documented. The time course, symptoms, and treatment are detailed in Table 2. Necrosis occurred only in patients with infratentorial primary tumors. The sites included the brainstem ($n = 5$), cerebellum ($n = 1$), and a combination of both brainstem and cerebellum ($n = 2$). One death was attributed to necrosis 24 months after the first imaging evidence of necrosis. Measured from the start of CSI, the median time to the first imaging evidence of necrosis was 4.8 months (range, 2.5–9.8 months), and for symptomatic necrosis it was 6.0 months (range, 4.2–7.9 months). The cumulative incidence of necrosis estimated at 5 years was $3.7\% \pm 1.3\%$ ($n = 236$) for the entire cohort and $4.4\% \pm 1.5\%$ ($n = 196$) for those with infratentorial tumors. With a prescribed cranial dose of 23.4 Gy ($n = 148$) and > 23.4 Gy ($n = 88$), the estimated 5-year cumulative incidence of necrosis was $2.7\% \pm 1.4\%$ for those with a prescribed cranial dose of 23.4 Gy ($n = 148$) and $5.3\% \pm 2.6\%$ for those receiving > 23.4 Gy ($n = 88$; $p = 0.4486$).

The mean relative volume of infratentorial brain (combined brainstem and cerebellum) receiving a radiation dose 50 Gy, 52 Gy, and 54 Gy was significantly higher for patients with necrosis, at $92.12\% \pm 4.58$, $88.95\% \pm 5.50$, and $82.28\% \pm 7.06$, compared with $72.89\% \pm 1.96$ ($p = 0.0337$), $69.16\% \pm 1.97$ ($p = 0.0275$), and $63.37\% \pm 1.96$ ($p = 0.0488$), respectively, for patients without necrosis (Fig 1). Logistic regression analysis yielded an odds ratio of 1.021 (95% CI: 0.996–1.047) for absolute and 1.026 (95% CI: 0.996–1.057) for risk of necrosis due to relative infratentorial volume receiving radiation dose 52 Gy. The relative volume of brain, brainstem, and spinal cord receiving radiation doses 50 Gy and up to 60 Gy was not statistically different for patients with and without necrosis. For patients with necrosis, the mean volume of infratentorial brain receiving 5000cGy, 5200cGy, and 5400cGy was 184.48mL, 178.96mL, and 167.32mL, respectively. For patients without necrosis, the mean volume of infratentorial brain receiving 5000cGy, 5200cGy, and 5400cGy was 131.21mL, 124.37mL, and 113.70mL. A subset analysis was performed for all patients with infratentorial tumors ($n = 195$) and patients with infratentorial tumors and high-risk disease ($n = 70$), but there were no significant predictors for necrosis from these subgroups. Age was also not found to be predictive of necrosis.

Necrosis was diagnosed with a combination of post-contrast T1-weighted MR enhancement and increased signal intensity on T2-weighted imaging in all 8 patients. MR spectroscopy was used to confirm necrosis in 3 of 8 patients. None of the patients underwent biopsy or were managed surgically. The time to symptoms from the first imaging evidence of necrosis ranged from <1 month to 3.5 months. Seven patients presented with neurologic symptoms, including new cranial neuropathies (4/8), quadriplegia (3/8), respiratory failure (4/8), dysphagia requiring gastrostomy tube placement (4/8), and tracheostomy with complete or partial mechanical ventilation dependence (4/8). Two patients developed new onset seizure disorders. Patients were treated with a combination of dexamethasone, bevacizumab, and hyperbaric oxygen therapy. Five of 8 patients developed metachronous enhancing lesions on follow-up imaging up to 6 years after the initial diagnosis of necrosis. Five patients had imaging resolution at a median time of 12.7 months (range, 6.4–84.6 months) after the diagnosis of necrosis. Two additional patients have not yet had imaging resolution 5.4 and 9.3 months after the diagnosis of necrosis. The estimated 5-year overall survival for all patients was $80.3\% \pm 3.5\%$.

Discussion

Impact of Patient and Clinical Factors

Although CNS embryonal tumors are the most common malignant brain tumors in children and large prospective clinical trials have been performed by cooperative groups, the incidence and risk factors for CNS necrosis are not precisely defined. The lack of information from historical series may be attributed to the low incidence and additional factors, including poor disease control, lack of long-term follow-up, and misdiagnosis.

Indeed, early medulloblastoma studies had gross total resection (GTR) rates of 36% to 46% (11) and poorer outcomes than with our 70.3% GTR and 17% near total resection rates from this analysis. Children who undergo more aggressive surgery are more likely to be injured before initiating adjuvant therapy and more likely to develop severe complications from therapy. Most studies do not account for additional clinical factors such as postoperative meningitis, number of surgical procedures, neurologic deficits, posterior fossa syndrome, and hydrocephalus requiring a CSF shunt or tumor-related factors including extent of tumor and brainstem invasion. The Children's Oncology Group (COG) performed a prospective study on the incidence and severity of cerebellar mutism syndrome (CMS) (12). They found that for average-risk patients, brainstem invasion and postoperative CNS infection correlated with the risk of CMS.

Clinical factors that influence brainstem toxicity are likely to affect the incidence of CNS necrosis. For ependymoma patients, brainstem toxicity is influenced by surgical morbidity and tumor extent (13). Similarly, surgical morbidity and prevalence of diabetes affects the degree of brainstem toxicity for patients with skull-based chordomas and chondrosarcomas (14). Three of our patients had brainstem invasion, and one had invasion of the left cerebellar peduncle noted in their operative reports; two patients required more than one surgical resection. Another patient required CSF shunting and underwent five shunt revisions before the diagnosis of necrosis. One patient had marked perioperative necrosis noted on imaging. Five patients had CMS, and four patients had postoperative meningitis. Each of these complicating factors may have reduced the threshold for these patients to develop necrosis.

Impact of Radiation Dose

We found that the percent of infratentorial brain receiving radiation doses 50 Gy, 52 Gy, and 54 Gy significantly predicted radiation necrosis in our patient population. We recommend dose constraints for the infratentorial brain as follows: the volume receiving 50 Gy should be no more than 73%, the volume receiving 52 Gy should be no more than 69%, and the volume receiving 54 Gy should be no more than 63%, based on the dose-volume histogram data of patients without necrosis. We anticipate < 1% risk of necrosis when these dose constraints are utilized for treatment planning for patients treated with aggressive surgical resection, CSI, and adjuvant chemotherapy.

One of the differences between our protocol and the current regimens used in the cooperative groups is the cumulative primary site dose of 55.8 Gy versus 54 Gy. Of note, 17 of the study patients received a prescribed primary site dose in excess of 55.8 Gy, and one of them developed necrosis. Given the high rate of survivorship, we may consider decreasing the total primary site dose to 54 Gy in future trials and using smaller CTV margins. We have used the dose-volume data from this series to create dose-volume histograms for the brain, brainstem, spinal cord, and infratentorial brain (Figure 2). These curves represent the dataset for which there is an estimated 3.7% incidence of necrosis. We offer this as a model for physicians to use when evaluating treatment plans and for future protocol development.

Higher radiation dose (15) and higher dose per fraction (16) have been associated with an increased risk of radiation necrosis. The prospective data most commonly referenced for rates of radiation necrosis come from a dose escalation study (50.4 Gy/28 fractions versus 64.8 Gy/36 fractions) for adult low-grade glioma in which the low-dose arm had an actuarial 2-year incidence of 2.5% grade 3 to 5 radiation necrosis compared with 5% in the high-dose arm.(17) Ruben et al. (15) reviewed more than 400 glioma patients and found that in addition to total radiation dose and dose per fraction, radiation necrosis was related to the biologic equivalent dose and subsequent chemotherapy and that patients were unlikely to develop cerebral necrosis at doses below 50 Gy in 25 fractions. Because all of our patients had similar dose-intense chemotherapy, we were unable to assess the impact of chemotherapy in our patients. However, our 3.7% incidence of necrosis is comparable to the published rates for adult glioma treated with 1.8 Gy per fraction.

Necrosis Diagnosis

The gold standard to diagnose radiation necrosis has been biopsy; however, surgical intervention may increase morbidity, especially when considering the brainstem and cerebellum. Several imaging modalities have been investigated for their ability to diagnose necrosis and distinguish between necrosis and recurrent tumor. These modalities include T1- and T2-weighted MRI, diffusion-tensor imaging, MR spectroscopy, and perfusion MR. We relied on serial changes, including increasing parenchymal enhancement on post-contrast T1 images and increasing volume of T2-weighted MR imaging signal abnormality. We found that resolution of necrosis can be a long process during which lesions can show signs of improvement followed by progression in the same or other sites before stabilizing. None of the patients with necrosis were diagnosed with recurrence.

White matter changes on follow-up MR imaging attributed to the combined effects of chemotherapy and radiation therapy appear to be prevalent in children with brain tumors. One series included 24 children treated with radiation therapy and high-dose chemotherapy reported an MRI lesion-free survival rate of $74\% \pm 6\%$ at 1 year and $57\% \pm 8\%$ at 2 years. (18) Understanding the relationship between white matter changes and radiation necrosis is important, because these changes may represent early necrosis. Perhaps when faced with early post-treatment imaging changes, a short follow-up with the best combination of imaging would help diagnose necrosis and enable early treatment intervention to reduce its sequelae.

Necrosis Treatment

Corticosteroids are considered frontline therapy for radiation necrosis and hyperbaric oxygen has been used adjunctively with mixed results (19). Recently, bevacizumab has shown promise as a treatment for radiation necrosis (20). Reducing vascular permeability has been postulated as the mechanism of action for bevacizumab.

Conclusions

Brain necrosis in patients with CNS embryonal tumors is an uncommon yet important side effect often leading to devastating neurologic consequences. When competing risk of death by any cause is considered, the cumulative incidence is 3.7% and may be higher in specific subgroups. The proportion of infratentorial brain volume receiving more than 50 Gy can be used to predict necrosis. Adherence to suggested dose constraints may reduce the incidence of necrosis for this patient population.

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Data from prospective trials was used to estimate the incidence and risk factors associated with CNS necrosis for children with embryonal tumors treated with surgery, craniospinal irradiation, and chemotherapy. The analysis predicts an incidence of 3.7% at 5 years. The proportion of infratentorial brain volume receiving more than 50 Gy is predictive of necrosis. These findings suggest adherence to dose constraints may reduce the incidence of necrosis for this patient population.

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Figure 1.
Infratentorial brain mean dose and volume curves for all patients (blue) and those with (maroon) and without (green) necrosis.

Figure 2. Brain (upper left), brainstem (upper right), infratentorial brain (lower left), and spinal cord (lower right) mean percent volume receiving specific radiation doses $\pm$ standard deviation for all patients included in this study.

Table 1

Patient and treatment characteristics.

	ALL PATIENTS NO(%)	PATIENTS WITHOUT NECROSIS NO(%)	PATIENTS WITH NECROSIS NO(%)
SEX			
Female	87 (36.86)	83 (36.40)	4 (50)
Male	149 (63.13)	145 (61.44)	4 (50)
RACE			
Asian	5 (2.12)	5 (2.19)	0
Asian and White	1 (0.42)	1 (0.44)	0
Black	34 (14.41)	30 (13.16)	4 (50)
Black and White	1 (0.42)	1 (0.44)	0
Multiple Race (NOS)	1 (0.42)	1 (0.44)	0
Other	14 (5.93)	14 (6.14)	0
White	180 (76.27)	176 (77.19)	4 (50)
DIAGNOSIS			
Medulloblastoma	186 (78.81)	179 (78.51)	7 (87.50)
AT/RT	24 (10.17)	23 (10.09)	1 (12.50)
SPNET	19 (8.05)	19 (8.33)	0
Pineoblastoma	7 (2.97)	7 (3.07)	0
RISK GROUP			
Average-Risk	148 (62.71)	144 (63.16)	4 (50)
High-Risk	88 (37.29)	84 (36.84)	4 (50)
LOCATION			
Infratentorial	195 (82.63)	187 (82.02)	8 (100)
Spinal cord	3 (1.27)	3 (1.32)	0
Supratentorial	38 (16.10)	38 (16.67)	0
EXTENT OF SURGERY			
Biopsy	6 (2.54)	6 (2.63)	0
STR	24 (10.17)	23 (10.09)	1 (12.50)
NTR	40 (16.95)	39 (17.11)	1 (12.50)

	ALL PATIENTS NO(%)	PATIENTS WITHOUT NECROSIS NO(%)	PATIENTS WITH NECROSIS NO(%)
GTR	166 (70.34)	160 (70.18)	6 (75.00)
NUMBER OF RESECTIONS			
1	181 (76.69)	175 (76.75)	6 (75.00)
>1	55 (23.31)	53 (23.25)	2 (25.00)
TOTAL	236	228	8

Table 2

Clinical characteristics of patients with necrosis

Age (yr)/Sex	Risk Group	Time to Necrosis Imaging	Time to Necrosis Symptomatic	Neurological Deficits	Grade	Treatments and Interventions	Time to Imaging Resolution
6.9/F	AR	9.8	NA	None	1	None	84.6
10.9/M	AR	2.5	6.1	CN Deficits	3	Dexamethasone HBOT, Gtube	7.1
10.7/F	AR	2.8	5.5	CN deficits	3	Dexamethasone HBOT, LMWH	53.2
5.4/M	HR	5.5	6.9	CN Deficits	3	Dexamethasone	6.3
9.0/F	HR	2.7	4.2	Respiratory Failure	4	Dexamethasone tracheostomy, Gtube	NA
6.7/F	HR	4.8	5.7	CN Deficits, Quadriplegia, Respiratory Failure	4	Dexamethasone HBOT, Bevacizumab, tracheostomy	NA
3.9/M	AR	4.9	7.9	Quadriplegia, Respiratory Failure	4	Dexamethasone Tracheostomy, Gtube	12.7
8.3/M	HR	5.0	6.0	Quadriplegia, Respiratory Failure	5	Dexamethasone Tracheostomy, Gtube	NA

Abbreviations: CN = cranial nerve HBOT = hyperbaric oxygen therapy; LMWH = low molecular weight heparin; AR = average-risk; HR = high-risk.