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CLINICAL STUDY

Proton therapy for adult medulloblastoma: Acute toxicity and disease control outcomes

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Abstract

Purpose We report disease control, survival outcomes, and treatment-related toxicity among adult medulloblastoma patients who received proton craniospinal irradiation (CSI) as part of multimodality therapy.

Methods We reviewed 20 adults with medulloblastoma (≥ 22 years old) who received postoperative proton CSI ± chemotherapy between 2008 and 2020. Patient, disease, and treatment details and prospectively obtained patient-reported acute CSI toxicities were collected. Acute hematologic data were analyzed.

Results Median age at diagnosis was 27 years; 45% of patients had high-risk disease; 75% received chemotherapy, most (65%) after CSI. Eight (40%) patients received concurrent vincristine with radiotherapy. Median CSI dose was 36GyE with a median tumor bed boost of 54GyE. Median duration of radiotherapy was 44 days. No acute ≥ grade 3 gastrointestinal or hematologic toxicities attributable to CSI occurred. Grade 2 nausea and vomiting affected 25% and 5% of patients, respectively, while 36% developed acute grade 2 hematologic toxicity (36% grade 2 leukopenia and 7% grade 2 neutropenia). Those receiving concurrent chemotherapy with CSI had a 38% rate of grade 2 hematologic toxicity compared to 33% among those not receiving concurrent chemotherapy. Among patients receiving adjuvant chemotherapy (n = 13), 100% completed ≥ 4 cycles and 85% completed all planned cycles. With a median follow-up of 3.1 years, 4-year actuarial local control, disease-free survival, and overall survival rates were 90%, 90%, and 95%, respectively.

Conclusions Proton CSI in adult medulloblastoma patients is very well tolerated and shows promising disease control and survival outcomes. These data support the standard use of proton CSI for adult medulloblastoma.

Keywords Craniospinal irradiation · Radiation therapy · Particle therapy · Central nervous system tumors · Clinical outcomes

Introduction

Medulloblastoma (MB) is a malignant brain tumor arising within the cerebellum. It is the most common malignant brain tumor in children; however, it is relatively rare in adults with an incidence of 0.6 per million, a tenfold decrease compared to the pediatric population [1]. In the United States, an estimated 150 cases are diagnosed annually in patients over 14 years old compared to ~ 300 cases in children 14 and younger (2). Of the post-pubertal cases, nearly 80% occur among patients ages 15–39 years old and the incidence is exceedingly rare in patients ≥ 40 years old (~ 30 cases annually) [2]. Because of the rarity of this malignancy in the adult population, there are limited prospective data and an absence of randomized data to help define the optimal treatment approach. Therefore, treatment paradigms

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for adults are generally adapted from the pediatric treatment regimen. Advances in molecular classification and subtyping have allowed more accurate prognosis of MB. However, there remain differences in outcomes between the pediatric and adult MB populations. Among the three primary adult subtypes—WNT, SHH, and group 4—adults with WNT and group 4 subtypes appear to have worse progression-free and overall survival outcomes compared to their pediatric counterparts, while pediatric and adult patients with SHH MB appear to have similar outcomes [3]. Consistent with pediatric treatment paradigms, the adult MB treatment regimen consists of surgical resection and postoperative craniospinal irradiation (CSI). Although surgery and CSI are universally adopted in adult MB, the indications for systemic therapy are less certain and thus chemotherapy is not as consistently utilized [4]. Proton radiotherapy has been used in an effort to reduce radiation risks associated with CSI and optimize multimodality therapy. With proton radiotherapy, charged particles can reduce the radiotherapy dose to surrounding normal tissue, in particular, extraneural organs (bone marrow, liver, lung, gastrointestinal tract) along the craniospinal axis and normal brain from the radiotherapy boost to the tumor bed. The physical properties of the proton beam and the Bragg Peak phenomena in eliminating the radiation beam's exit dose underlie the clinical benefits to proton therapy. The use of proton therapy for CSI in pediatric MB has been intensively studied, widely adopted, and incorporated into ongoing cooperative group trials (NCT01878617, NCT02724579) [5, 6] Less is known about the role and utility of proton CSI in adult MB, with only a single outcome study on the subject [7]. Here we report the largest series to date detailing the disease control and survival outcomes for adult patients with MB treated with proton CSI. Additionally, we review acute toxicities during proton CSI, and describe the feasibility of completing planned adjuvant chemotherapy after proton CSI.

Methods

We retrospectively analyzed the medical records of 20 adult patients (age ≥ 22 years) with newly diagnosed MB treated with proton CSI at the University of Florida Health Proton Therapy Institute between the years 2008 and 2020. The age of 22 years was used as the cutoff for inclusion because patients ≤ 21 years at the time of radiotherapy were treated in our pediatric program. All patients provided written informed consent for enrollment on a prospective, institutional review board-approved outcomes tracking protocol (IRB201703048). No patient had received prior radiotherapy. All patients had pathologic confirmation of MB. Patient and tumor characteristics, treatment details, and follow-up information were obtained from the medical record. For patients unable to return to our facility for follow-up, we obtained outside clinical and radiology records for follow-up details. The date of diagnosis was the date of pathologic confirmation of MB. Disease subtyping was obtained from patient records, including immunohistochemical staining, molecular cytogenetics, and next-generation sequencing when available. Staging was documented according to the Chang staging system for medulloblastoma.

Radiotherapy treatment

Patients were simulated using a 3-dimensional (3D) computed tomography (CT) scan. Between 2008 and 2018, patients underwent simulation for CSI in the prone position. In 2019, we modified our treatment planning to accommodate supine CSI. All tumor/tumor bed boost plans were delivered in the supine position with an aquaplast mask and bite piece. Treatment was delivered utilizing double-scattered (DS) proton therapy until 2020 at which time our institution converted to pencil-beam scanning (PBS) CSI plans (2 patients in the current study). Target delineation was informed by the co-registration of contrast-enhanced pre- and postoperative magnetic resonance imaging (MRI) to the radiation planning CT scan. Clinical target volumes (CTVs) were generated as follows: "CTV_CSI" was generated by combining "CTV_Brain" and "CTV_Spine," which included the complete neuroaxis contained within the meninges and the skull base foramen with extension inferiorly to include the conus medullaris and sacral nerve roots. CTV_CSI was identical for the DS and PBS plans. The planning target volume (PTV) expansion of CTV_Spine varied slightly between the DS and PBS plans. For both modalities, "PTV_Brain" was generated by adding a 3-mm isotropic expansion to the whole-brain portion of CTV_CSI. For the DS plans, a 5-mm isotropic expansion was added to CTV_Spine while, for PBS, a 5-mm radial expansion and 7-mm superior/inferior expansion was used for the CTV_Spine. Target delineation for the boost phase was the gross tumor volume (GTV), which included the tumor resection bed and gross residual tumor plus a 1-cm isotropic CTV expansion (limited by barriers of tumor spread) and a 3-mm PTV expansion. The DS CSI plan consisted of lateral opposed whole-brain fields matched to 2–3 posterior-anterior spine fields depending on the height of the patient. Spine field match sites were feathered by shifting the spine fields after ~ every 8 fractions of CSI. The tumor bed boost was delivered using 2–3 fields arranged for optimal dose delivery and as much avoidance as possible of proton fields with an end-of-range in the brainstem. The PBS CSI plans were delivered entirely using PA fields (including the whole brain portion of treatment) with matching spine fields feathered using dose modulation. Because all of the patients in this cohort were adults with fully or near fully-developed

skeletons at the time of radiotherapy, no effort was made to uniformly distribute radiation dose across vertebral bodies as is routinely done in pediatric/adolescent proton CSI. The PBS boost plans utilized 3 fields with only one field ending on a critical organ at risk (Supplementary Figure S1). Daily orthogonal x-rays and/or CBCT were used for daily image guidance.

No patient in this series was given prophylactic medication for nausea or vomiting prior to the start of radiotherapy. Two patients with nausea/vomiting prior to the start of radiotherapy were taking anti-emetics at the time CSI began.

Chemotherapy

Because we are a national and international referral center for proton therapy, many of our patients received chemotherapy per their home institution's standards. The chemotherapy regimen in our patient cohort reflects the diversity of contemporary treatments across the United States, the United Kingdom, and the rest of Europe.

Patient follow-up

Patients were recommended clinical follow-up and imaging of the sites of gross disease 1 month after radiotherapy, followed by clinical follow-up and a brain MRI Brain (and spine MRI if there is gross spine disease at diagnosis) every 3–4 months for 3 years after treatment, then extended to every 6 months until 5 years after radiotherapy, and annually thereafter. Complete neuroaxis imaging was recommended annually for all patients regardless of M stage at diagnosis. Annual pituitary function labs and ophthalmology follow-up were recommended.

Acute toxicity evaluation

Acute toxicities were prospectively evaluated during weekly on-treatment visits according to the Common Terminology Criteria for Adverse Events (CTCAE). Patients treated prior to 2011 (n = 3) were evaluated using CTCAE version 3 and all other patients were prospectively evaluated using CTCAE version 4. Hematologic toxicities were retrospectively evaluated based on available complete blood count (CBC) data during and immediately following completion of CSI. Acute hematologic toxicities were scored using CTCAE version 4. Patients receiving concurrent chemotherapy with CSI had CBC with differentials (diff) performed at baseline, weekly or biweekly during chemoradiation, and upon completing radiotherapy. Patients not receiving concurrent chemoradiotherapy had CBC with diff at baseline and again upon completing radiotherapy. Three patients receiving radiotherapy alone did not have CBC data available and were not included in the analysis for hematologic toxicity.

Statistics

JMP Pro version 15.0.0 was used for statistical analysis (SAS Institute, Cary, NC). Basic descriptive statistics are provided for this series. Medians were used to estimate the center of a continuous distribution rather than mean to avoid outliers overly influencing the estimate. The Kaplan–Meier product-limit method was used to estimate disease-free and overall survival at 4 years following diagnosis. Survival outcomes were measured from the date of diagnosis to the date of death and/or radiographic confirmation of disease recurrence.

Results

Patients and treatment

Twenty consecutive adult patients with MB treated with proton CSI were included. Patient, disease, and treatment characteristics are detailed in Table 1. The median age at the time of diagnosis was 27 years (range, 22–30 years). Nearly half of the patients (45%) had high-risk disease: 4 patients due to gross residual disease at the primary site ($\geq 1.5 cm^2$), 4 patients due to neuroaxis metastases (M3, 3 patients; M1, 1 patient), and 1 patient for both gross residual disease and presence of neuroaxis metastases at diagnosis. Only 11 patients underwent molecular subtyping of tumor and included WNT (n = 2; 20%), SHH (n = 8; 80%), and Group 4 (n = 1; 10%). Large cell/anaplastic histology was not considered a high-risk feature independent of the other risk factors (i.e., gross residual disease and/or metastases). One of the 2 patients with large cell/anaplastic histology was classified as high-risk due to residual tumor and M3 disease.

The radiotherapy treatment details are described in Table 1. All patients received proton therapy. Excluding the 2 patients who received neoadjuvant chemotherapy prior to radiotherapy, the median time from surgery to beginning CSI was 34 days (range, 23 – 80 days). The median CSI dose was 36 GyE (range, 23.4–36.0 GyE) with a median tumor bed boost of 18 GyE (range, 18–30.6 days), for a median cumulative dose of 54 GyE (range, 54–55.8 GyE). All but 3 patients received 36 GyE CSI. The 3 patients who received lower doses received either 23.4 GyE (n = 2) or 30.6 GyE (n = 1) and were classified as standard-risk. Two patients received a tumor bed boost up to 55.8 GyE.

The timing of chemotherapy relative to CSI is detailed in Table 1. Twenty-five percent of patients received no chemotherapy (4 standard-risk and 1 high-risk). Forty percent of patients received concurrent weekly vincristine with craniospinal irradiation. Most patients received adjuvant chemotherapy after CSI (65%), either neoadjuvant and adjuvant (5%), concurrent and adjuvant (35%) or adjuvant only (25%).

Table 1 Patient, disease, and treatment characteristics (N = 20)

Characteristics	Number of patients (%) or other value
Median age (range)	27 (22–30) years
Sex	
Male	10 (50%) pts
Female	10 (50%) pts
T stage	
T1	1 (5%) pts
T2	13 (65%) pts
T3	6 (30%) pts
T4	0 pts
M stage	
M0	15 (75%) pts
M1	1 (5%) pts
M2	2 (10%) pts
M3	2 (10%) pts
M4	0 pts
Extent of surgery	
Gross total resection	12 (60%) pts
Subtotal resection < 1.5 cm residual	3 (15%) pts
Subtotal resection ≥ 1.5 cm residual	5 (25%) pts
Risk group	
Standard	11 (55%) pts
High	9 (45%) pts
Histology	
Classical	12 (60% pts
Desmoplastic	6 (30%) pts
Anaplastic	2 (10%) pts
Molecular subtype	
WNT	2 (10%) pts
SHH	8 (40%) pts
Group 4	1 (5%) pts
Unknown	9 (45%) pts
Radiation therapy	
Median craniospinal irradiation dose (range)	36 (23.4–36) GyE
Median primary tumor boost dose (range)	18 (18–30.6) GyE
Median total dose (range)	54 (54–55.8) GyE
Mean elapsed treatment days (range)	44 (40–49) days
Chemotherapy	
Any chemotherapy	15 (75%) pts
Preradiotherapy chemotherapy only	1 (5%) pt
Preradiotherapy and adjuvant chemotherapy	1 (5%) pt
Concurrent chemotherapy only	1 (5%) pt
Adjuvant chemotherapy only	5 (25%) pts
Concurrent and adjuvant chemotherapy	7 (35%) pts
No chemotherapy	5 (25%) pts
Number of adjuvant chemotherapy cycles completed	
≥ 4	13 (100%) pts
≥ 5	8 (62%) pts
≥ 6	7 (54%) pts
≥ 7	4 (31%) pts
≥ 8	4 (31%) pts
≥ 9	1 (8%) pts

Disease control and survival outcomes

With a median clinical follow-up time of 3.1 years (range, 0.6–12.7 years) and median radiographic follow-up time of 2.4 years (range, 0.3–12.7 years), the actuarial 4-year local control, disease-free survival, and overall survival rates were 90% (95% CI 53–99), 90% (95% CI 53–99), and 95% (95% CI 72–99), respectively (Fig. 1). One patient died 6 months after completing CSI due to complications from hematologic toxicity after completing adjuvant chemotherapy. This patient also received neoadjuvant chemotherapy. He had no evidence of disease at the time of death. Only 2 of 20 patients experienced disease recurrence. Both patients had standard-risk disease and local failures in the tumor bed. One of these patients received 36 GyE CSI and a tumor bed boost to 54 GyE with concurrent weekly vincristine. He received no additional chemotherapy. He developed a local recurrence 38 months after radiotherapy and died from disease progression 57 months after treatment (Supplementary Figure S2). The second patient received 30.6 GyE CSI and a tumor bed boost to 54 GyE (without concurrent chemotherapy) followed by 9 cycles of adjuvant chemotherapy. He developed a tumor bed recurrence 57 months after radiotherapy and received salvage surgery and postoperative proton reirradiation with concurrent temozolomide followed

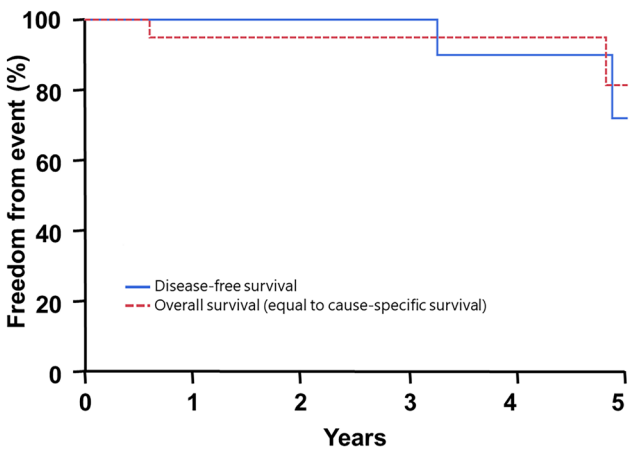

Fig. 1 Kaplan–Meier curve for overall survival and disease-free survival

by chemotherapy. He experienced a second posterior fossa recurrence with an intracranial metastasis 43 months after reirradiation and underwent salvage resection followed by high-dose chemotherapy with autologous stem cell transplant. He is alive with no evidence of disease 10 years after his initial diagnosis.

Acute CSI toxicities

The acute radiotherapy-related toxicities among our cohort are described in Table 2. The most common ≥ grade 2 acute toxicities were radiation dermatitis and fatigue in 4 patients (20%) each. The only acute ≥ grade 3 toxicity was 1 patient (5%) who experienced grade 3 fatigue.

Five patients (25%) experienced grade 2 nausea and 1 patient (5%) experienced grade 2 vomiting. Three patients (15%) had weight loss greater than 5% during radiation treatment, but none had weight loss ≥ 10% of their body weight. Five patients (25%) reported grade 2 anorexia.

Hematologic toxicities

All 8 patients who received concurrent vincristine with CSI had CBC data available. Eight of 12 patients who did not receive concurrent chemotherapy with CSI had CBC data available. Two of these patients received preradiotherapy chemotherapy and had baseline ≥ grade 3 hematologic toxicities at the start of CSI, and were excluded from the hematologic toxicity analysis (final n = 6). Among the 8 patients receiving concurrent vincristine with CSI, 3 patients (38%) experienced grade 2 hematologic toxicities (including 3 patients with grade 2 leukopenia, 1 of whom also developed grade 2 neutropenia). Of the 6 patients who did not receive concurrent chemotherapy, the only ≥ grade 2 acute hematologic toxicities were 2 patients (33%) with grade 2 leukopenia. There were no ≥ grade 3 acute hematologic toxicities due to CSI. In total, among the 14 patients included in this analysis, 5 patients (36%) developed acute grade 2 hematologic side effects during or immediately after radiotherapy (4 patients with grade 2 leukopenia and 1 patient with both grade 2 leukopenia and grade 2 neutropenia). No patient had ≥ grade 2 thrombocytopenia.

Table 2 Reported acute toxicities during radiotherapy (CTCAE v4.0)

Toxicities	Grade 2	≥ Grade 3
Gastrointestinal (n = 20)		
Anorexia	5	0
Nausea	5	0
Vomiting	1	0
Weight Loss	0	0
Hematologic (n = 14)		
Anemia	0	0
Thrombocytopenia	0	0
Leukopenia	5	0
Neutropenia	1	0

Treatment interruptions

The median number of elapsed treatment days during radiotherapy was 44 (range, 40–49 days). Two patients required treatment breaks during radiotherapy. One required a treatment break of 3 days in the first week of CSI due to baseline hematologic toxicity at the start of CSI from pre-RT chemo (number of elapsed treatment days, 47). A second patient had a 2-day treatment break due to nausea and headaches (number of elapsed treatment days, 44).

Chemotherapy completion

All 8 patients who received concurrent chemotherapy during CSI completed 6 cycles of weekly vincristine. Due to variations in adjuvant chemotherapy regimen, there were wide differences in the planned number of cycles among those receiving adjuvant chemotherapy (range, 4–9). Among the 13 patients receiving adjuvant chemotherapy, 11 (85%) completed all of their planned cycles (Table 1). One patient discontinued chemotherapy due to severe hematologic toxicities after completing 5 of 6 planned cycles (after receiving 2 cycles of chemotherapy prior to radiation). Another patient discontinued adjuvant chemotherapy after completing 6 of 8 planned cycles due to poor tolerance and patient preference. Seven patients (54%) completed their prescribed adjuvant chemotherapy without chemotherapy dose reductions. Hematologic toxicity was the basis for dose reduction in 2 patients.

Discussion

Our study examines disease control and survival outcomes, rates of acute radiotherapy-related toxicities, and completion rates of adjuvant chemotherapy for adult MB patients treated with proton CSI. Our disease-related outcomes demonstrating 4-year local control, progression-free survival, and overall survival of 90%, 90% and 95%, respectively, compare favorably to data from modern prospective adult series [8–10].Our data support the safety and efficacy of proton CSI for disease control. Notably, at the time of analysis, none of our patients with M + disease had failed in the spine, alleviating technical concerns about the risk of match line cold spots due to proton delivery techniques. Our radiation-related toxicity data indicate that proton CSI is well-tolerated in this unique patient population. In improving the patient tolerance of CSI and reducing acute gastrointestinal

and hematologic toxicity of radiotherapy, there are two significant disease control benefits that may be conferred by proton CSI including reduced radiotherapy treatment breaks due to preserved bone marrow function and improved tolerance/completion of adjuvant chemotherapy.

Numerous series have suggested an influence of overall CSI treatment duration on disease control outcomes. Local tumor control, disease-free survival, and overall survival appear to be impacted by the total duration of radiotherapy, with a treatment duration goal of < 45 to 49 days [11–15]. The vast majority of treatment interruptions during CSI are attributable to hematologic toxicity. Kumar et al. evaluated the rates of acute hematologic toxicity and impact on CSI treatment interruptions in 52 children and adults with MB treated using 3D conformal x-ray radiotherapy without concurrent chemotherapy [16]. They reported spinal radiation field treatment interruptions in over 70% of patients due to hematologic toxicity (primarily leukopenia). Their rates of grade 2 and grade 3 leukopenia was 50% and 19%, respectively. Grade 2 anemia and grade 2 thrombocytopenia both affected 6% of patients. The median treatment interruption length was 9 days and 25% of patients had CSI durations of ≥ 50 days [16]. The prospective NOA-07 trial included only adult MB patients treated with concurrent vincristine and CSI. Beier et al. reported rates of acute grade 3/4 leukopenia, anemia, and thrombocytopenia during chemoradiotherapy of 36.7%, 13.3%, and 3.3%, respectively. In contrast, in our proton-CSI series, there were no cases of ≥ grade 3 hematologic toxicity. The rates of grade 2 leukopenia, neutropenia, anemia, and thrombocytopenia in our series were 36%, 7%, 0%, and 0%, respectively. Only 2 patients (10%) had radiotherapy treatment interruptions, the longest being 3 days (in a patient who received neo-adjuvant chemotherapy and had grade 4 neutropenia, grade 4 leukopenia, and grade 2 anemia at the start of CSI). Notably, all of the patients in our series completed radiation in less than 50 days (median 44 days, range: 40–49). Our toxicity data are very similar to the proton CSI series for adult MB from MD Anderson Cancer Center. In their retrospective series, Brown et al. reported grade 2 and 3 leukopenia of 56% and 0%, respectively and grade 2 anemia (by RTOG acute toxicity score) and thrombocytopenia of 11% and 6%, respectively. In a larger series from the same group, including adult patients with various malignancies treated with proton CSI (with or without concurrent chemotherapy), they reported rates of grade 3 leukopenia, anemia, and thrombocytopenia of 9%, 0%, and 2%, respectively. Grade 2 events occurred at rates of 43%, 15%, and 2%, respectively. Our data also support the findings of a recent large cohort comparison in the pediatric MB population among patients receiving either proton or photon CSI. In their multi-institutional comparative analysis, Liu et al. demonstrated proton CSI compared to photon CSI correlated with significantly lower rates of grade ≥ 3 leukopenia (36.7% versus 54.1%), grade ≥ 3 lymphopenia (76.9% versus 100%), grade ≥ 2 anemia (35% versus 56.7%), and grade ≥ 1 thrombocytopenia (28.3% versus 45.9%) [17].

An important factor affecting treatment tolerance and CSI treatment interruptions is gastrointestinal toxicity. Proton CSI may lessen the severity of gastrointestinal toxicity by reducing dose to the upper and lower gastrointestinal organs (esophagus, stomach, and intestines). Brown et al. reported significantly less grade 2 nausea/vomiting (26% versus 71%) and weight loss of 5–10% (16% versus 57%) in patients receiving proton CSI versus their x-ray cohort [8]. Our data show very similar gastrointestinal toxicity outcomes with proton CSI, including no ≥ grade 3 gastrointestinal toxicities, and rates of grade 2 nausea and vomiting of 25% and 5%, respectively. Fifteen percent of patients lost greater than 5% of their baseline weight, but none lost 10%.

In addition to lengthening the radiotherapy duration, hematologic toxicities can impair the ability of patients to complete adjuvant chemotherapy. As described in multiple studies, myelosuppression is a common cause for patients to receive reduced or incomplete adjuvant chemotherapy. Furthermore, baseline blood cell counts correlate to hematologic toxicities and suboptimal chemotherapy dosing [18, 19]. The ability to preserve hematologic function during CSI for subsequent chemotherapy may be an of advantage for proton beam radiotherapy. The vertebral body-sparing effects of proton CSI reduce the amount of radiation received by the radiosensitive bone marrow. While a definite benefit of adjuvant chemotherapy on disease control and survival outcomes has not been established in adult MB patients (in contrast to pediatric patients), several retrospective and database studies suggest improvements in survival with chemotherapy [20–22]. In a retrospective cohort comparison of average-risk adult MB patients treated with or without adjuvant chemotherapy, Franceschi et al. showed significant improvement in progression-free and overall survival in the adjuvant chemotherapy cohort [23]. Notably, the progression-free and overall survival benefits of chemotherapy did not become apparent until 10 years after treatment. Kann et al. conducted a National Cancer Database analysis for adult MB patients, which also showed a survival benefit among all patients receiving adjuvant chemotherapy [24]. In a subset analysis, the benefit of adjuvant chemotherapy remained significant in patients with M0 disease, even those receiving full-dose CSI (36 Gy).

The NOA-07 study prospectively assessed the toxicity and feasibility of radio-polychemotherapy in adult MB patients, including a primary endpoint of a completion rate of at least 4 cycles of 8 planned cycles of adjuvant chemotherapy following x-ray-based CSI with concurrent vincristine. Beier et al. reported that 70% of patients completed at least 4 cycles of post-CSI chemotherapy and fewer than 40% completed all planned adjuvant chemotherapy. Our series

compares very favorably, with 100% of patients planned to receive adjuvant chemotherapy completing at least 4 cycles and 85% completing all planned adjuvant chemotherapy (median, 5 cycles).

Advanced x-ray radiotherapy techniques developed in the past several decades, including intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), have significantly improved our ability to deliver highly conformal radiation with improved dose avoidance of nearby organs at risk. These advanced techniques enable CSI delivery without field junction matching (as required with 3D conformal radiotherapy) with improved target coverage and dose homogeneity [25–27]. However, these x-ray-based techniques deliver a low to moderate radiation dose bath to much of the body tissues, including significant volumes of bone marrow, likely contributing to hematologic toxicity due to damage to bone marrow progenitor cells [26–28]. In contrast, proton CSI partially spares the vertebral column from receiving radiation and completely avoids other bone marrow sources such as the sternum and pelvis (**Fig. 2**). Another potential hematologic benefit of proton CSI compared to 3D conformal radiotherapy and especially IMRT/VMAT CSI is preservation of circulating lymphocytes through avoidance of the heart, aorta, spleen, and other major blood vessels. Given the expanse of body tissue treated in CSI and the exquisite radiosensitivity of circulating lymphocytes, the significant reduction of integral dose with protons can reduce the impact of radiation-related lymphopenia during CSI [29, 30]. As has been shown in other solid tumors, CSI-associated lymphopenia is associated with increased rates of tumor recurrence and worse overall survival in pediatric MB patients [30].

Beyond the benefits of proton CSI on acute toxicity reduction that may impact disease control and survival outcomes, proton CSI will likely reduce late treatment-related complications. As has been demonstrated in numerous dosimetric studies, proton CSI reduces the dose to the thyroid gland, heart, lungs, liver, kidneys, gastrointestinal tract, breast tissue, and pelvis [31, 32]. Especially in this young adult population with a high likelihood of long-term survival,

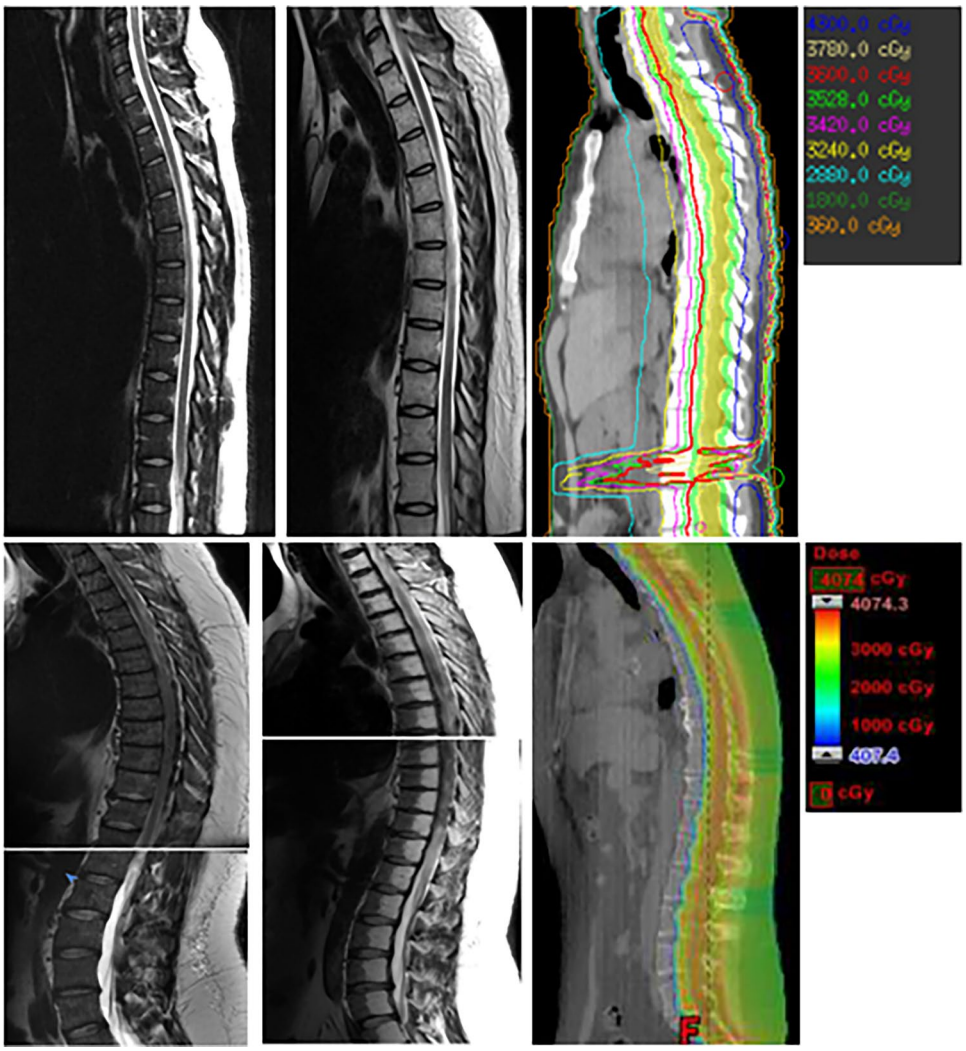

Fig. 2 Radiographic bone marrow comparison after x-ray craniospinal irradiation (CSI; top row) and proton CSI (bottom row). A patient treated with 3D conformal x-ray-based CSI to 36 GyE (upper row) and a patient treated with passively scattered proton CSI to 36 GyE (lower row) are shown. In each row, the image on the left was taken before CSI, the middle image occurred after CSI, and the right image is the radiation dose distribution (with corresponding dosage in cGy with colors in the right corner). Increased T2 signal in the vertebral bodies indicates radiotherapy-related bone marrow changes. Diffuse bone marrow signal changes seen throughout the T- and L-spine after x-ray CSI compared to partial sparing with proton CSI

minimizing radiation-induced malignancies and long-term treatment complications is paramount. Particularly relevant for this patient population, young adulthood may be the peak risk of radiation-associated breast carcinogenesis. IMRT/VMAT radiation techniques expose far more breast tissue to radiation compared to both 3D conformal radiotherapy and proton CSI.

While the current study suffers from the weaknesses inherent to any retrospective series, we believe it contributes much-needed data to a rare disease entity in adults. To date, no prospective randomized trial has been completed in adult MB patients. We rely on extrapolation from pediatric MB trials, few small prospective series, and retrospective studies to advance our understanding of the disease and improve treatment. Fortunately, the European Organisation for Research and Treatment of Cancer (EORTC) has developed a phase 2 randomized trial in post-pubertal/adult patients with newly diagnosed MB, EORTC-1634-BTG, which treats patients by molecularly classified subtype [33]. This trial includes randomizations to CSI dose de-intensification in patients with standard-risk disease as well as targeted drug therapy in those with the SHH subtype. It includes both concurrent and adjuvant chemotherapy. As this trial expands into the United States, there is interest by the NRG in a comparative analysis of proton versus x-ray therapy. Hopefully, this trial will provide critical data to refine our treatment and lend additional insight into differences in outcomes between proton and x-ray-based radiotherapy treatment for this malignancy.

Conclusions

Our study shows very good disease control and survival outcomes in adult patients with MB treated with proton CSI. Patients tolerated proton CSI without significant acute radiation-related toxicities. The low rates of gastrointestinal and hematologic toxicity during proton CSI may prevent unplanned treatment breaks during radiotherapy and may facilitate the completion of adjuvant chemotherapy. These data coupled with other studies support the standard use of protons for CSI in the treatment of adult MB.

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Data Availability The authors agree to share anonymized data upon reasonable request by researchers.

Declarations

Conflict of Interest The authors declare they have no conflicts of interest.

Ethical approval This retrospective study was approved by the University of Florida Institutional Review Board.

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