INTERNATIONAL JOURNAL of PARTICLE THERAPY

Referral Patterns and Treatment Delays in Medulloblastoma: A Large Academic Proton Center Experience

Sean M. Liu, BA[1]; Eric D. Brooks, MD[1,2,3]; M. Laura Rubin, PhD[1]; MD Anderson Cancer Center Radiation Oncology Fellows Consortium; David R. Grosshans, MD, PhD[1,2]; Steven J. Frank, MD[1,2], Mary Frances McAleer, MD[1,2]; Susan L. McGovern, MD, PhD[1,2]; Arnold C. Paulino, MD[1,2]; Kristina D. Woodhouse, MD[1,2]

[1]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2]Proton Therapy Center, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[3]University of Florida Health Proton Therapy Institute, Jacksonville, FL, USA

Abstract

Purpose: Patient travel time can cause treatment delays when providers and families decide to seek proton therapy. We examined whether travel distance or referral pattern (domestic versus international) affects time to radiation therapy and subsequent disease outcomes in patients with medulloblastoma at a large academic proton center.

Patients and Methods: Children with medulloblastoma treated at MD Anderson (MDA) with a protocol of proton beam therapy (PBT) between January 4, 2007, and June 25, 2014, were included in the analysis. The Wilcoxon rank-sum test was used to study the association between time to start of radiation and distance. Classification- and regression-tree analyses were used to explore binary thresholds for continuous covariates (ie, distance). Failure-free survival was defined as the time interval between end of radiation and failure or death.

Results: 96 patients were included in the analysis: 17 were international (18%); 19 (20%) were from Houston, Texas; 21 were from other cities inside Texas (21%); and 39 (41%) were from other US states. The median time from surgery to start of radiation was not significantly different for international patients (median = 1.45 months) compared with US patients (median = 1.15 months; $P = .13$). However, time from surgery to start of radiation was significantly longer for patients residing $>$ 1716 km ($>$ 1066 miles) from MDA (median = 1.31 months) than for patients residing $\leq$ 1716 km ($\leq$ 1066 miles) from MDA (median = 1.05 months; $P = .01$). This 1- to 2-week delay (median = 7.8 days) did not affect failure-free survival (hazard ratio = 1.34; $P = .43$).

Conclusion: We found that short delays in proton access can exist for patients traveling long distances to proton centers. However, in this study, treatment delays did not affect outcomes. This highlights the appropriateness of PBT in the face of travel coordination. Investment by proton centers in a rigorous intake process is justified to offer timely access to curative PBT.

Keywords: medulloblastoma; proton; travel; distance; delay

Submitted 25 Jul 2020
Accepted 13 Aug 2020
Published 31 Dec 2020

Corresponding Author:
Kristina D. Woodhouse, MD
Department of Radiation Oncology
The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030-4008, USA
Phone: +1 (877) 632-6789
kdwoodhouse@mdanderson.org

Original Article

DOI
10.14338/IJPT-20-00038.1

http://theijpt.org

Introduction

Medulloblastoma is one of the most common pediatric cancers and the most common pediatric malignant brain tumor, accounting for approximately 10% of all primary pediatric central nervous system tumors [1, 2]. Treatment for medulloblastoma has evolved in recent decades, most significantly with the development of trials exploring systemic-agent assignment based on tumor molecular subgroups [3, 4] and with proton therapy becoming a mainstay of treatment for craniospinal irradiation (CSI). Proton therapy is favored over photon radiotherapy in medulloblastoma because proton therapy can preserve surrounding structures in the nervous system; can avoid radiation exposure to healthy tissues, such as the heart, stomach, thyroid, lungs, reproductive organs, and intestines; and can reduce long-term treatment-induced toxicity [5–10].

Radiation is central to the treatment of medulloblastoma and is typically recommended to initiate within 4 weeks following surgical resection. In general, delays in treatment of cancer can result in significant compromises in outcomes, although this has not been well studied in patients with medulloblastoma [11–13]. Delays in treatment are particularly relevant to patients with medulloblastoma because of the low availability of proton therapy centers in the United States. There are fewer than 50 centers in operation, under construction, or in development in the United States, so many patients must travel long distances to receive proton therapy [14]. However, there is no information available, to our knowledge, studying the association between patients with medulloblastoma who must travel long distances to receive treatment and their overall outcomes in comparison to patients within close proximity of a proton center. Data that currently exist suggests inconclusive evidence that increased distance to health care treatment location affects general outcomes [15–17].

To address this gap in knowledge, we retrospectively examined our pediatric patients with medulloblastoma enrolled in trials at MD Anderson (MDA) to determine whether patient travel was associated with treatment delays or if timely access to care and clinical outcomes are associated with such delays.

Materials and Methods

Children with medulloblastoma consecutively treated at our proton center between January 4, 2007, and June 25, 2014, were included in the analysis (N = 96). All children were treated on prospective trials. However, those patients treated on protocols without primary endpoints yet reported were excluded to preserve outcomes reporting (n = 39 of 135; 29%). Patient demographics, clinical characteristics, and outcomes were summarized through descriptive statistics. Event-chart plots were used to visualize time from surgery to radiation start for each patient by location. Wilcoxon rank-sum test was used to study the association between continuous and dichotomous variables. Classification- and regression-tree analyses (CARTs) were used to assess whether a given distance threshold existed that led to delays in treatment start. Briefly, CART is a machine-learning technique that recursively partitions a covariate space by doing binary splits, producing groups that are as homogeneous as possible with respect to an outcome of interest [18]. To determine whether travel led to delays that subsequently affected medulloblastoma outcomes, we assessed whether longer distances were associated with shorter failure-free survival (FFS). The FFS was defined as the time interval between end of radiation and failure or death, whichever occurred first, censored at the last follow-up date for patients who neither failed nor died. Failure was defined as first imaging evidence of tumor progression or recurrence. Survival curves were estimated by the Kaplan-Meier method. Cox proportional hazard-regression models were used to test the effect of risk factors on survival (two-sided Wald tests) and to estimate effect sizes of risk factors. Statistical analyses were conducted in R (version 3.4.2, Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $P < .05$.

Results

A total of 96 patients were included in the study. The median follow-up time for patients alive during the study period after the end of radiation therapy was 42.9 months (95% confidence interval [CI], 31.1-57.1). The median age at diagnosis was 6 years (range, 1-17), 59% of the patients were male (n = 57), and 68% of the patients were white (n = 65). The most common histologies were classic medulloblastoma (n = 52; 54.2%) and anaplastic medulloblastoma (n = 24; 25%). Sixty patients (62.5%) belonged to the average-risk group, and 36 (37.5%) to the high-risk group. Seventy-one patients (74%) had gross total resections, 23 (24%) had subtotal resections (24%), and 2 biopsy (2%). All patients (100%) received curative-intent proton therapy, with almost all receiving CSI plus boost (n = 87; 90.6%), whereas a few patients (n = 9; 9.4%) received PBT to the tumor bed alone. Twenty patients (21%) died during the study period, and among those who died, the most common cause of death was tumor (n = 19; 95%). A complete summary of overall patient characteristics is presented in **Table 1**.

Table 1. Patient demographics and clinical characteristics.

Patient characteristics	Results; N = 96
Sex, No. (%)	
Female	39 (40.6)
Male	57 (59.4)
Race, No. (%)	
Hispanic	14 (14.6)
White	65 (67.7)
Black	4 (4.2)
Asian	4 (4.2)
Unknown	9 (9.4)
Age at time of diagnosis (y), median (min, max)	6 (1, 17)
Distance from MDA, km (miles)(median min, max)	1622 (1008) (1, 9362)
State, No. (%)	
AK	1 (1.0)
AZ	2 (2.1)
CA	3 (3.1)
CO	1 (1.0)
FL	1 (1.0)
GA	1 (1.0)
HI	1 (1.0)
IA	1 (1.0)
IL	4 (4.2)
KY	1 (1.04)
LA	1 (1.0)
MD	1 (1.0)
MI	4 (4.2)
MN	1 (1.0)
MO	2 (2.1)
NE	2 (2.1)
NY	1 (1.0)
PA	4 (4.2)
TX	39 (40.6)
VA	1 (1.0)
WA	4 (4.2)
WI	3 (3.1)
International	17 (17.7)
Country, No. (%)	
Australia	2 (2.1)
Cayman Islands	1 (1.0)
Denmark	8 (8.3)
Japan	1 (1.0)
Kuwait	1 (1.0)
Peru	1 (1.0)
Turkey	1 (1.0)
UAE	2 (2.1)
United States	79 (82.3)
Histology, No. (%)	
Anaplastic	24 (25.0)
Desmoplastic	9 (9.4)
Large cell	1 (1.0)
Medulloblastoma classical	52 (54.2)
Other	10 (10.4)

Table 1. Continued.

Patient characteristics	Results; N = 96
M stage, No. (%)	
0	60 (62.5)
1	2 (2.1)
2	10 (10.4)
3	23 (24.0)
4	1 (1.0)
Risk group, No. (%)	
Average risk	60 (62.5)
High risk	36 (37.5)
Surgery type, No. (%)	
Biopsy	2 (2.1)
GTR	71 (74.0)
STR	23 (24.0)
Proton modality, No. (%)	
Passive scatter	96 (100)
Boost type, No. (%)	
Not given	1 (1.0)
Posterior fossa	12 (12.5)
Tumor bed	83 (86.5)
Complete, all prescribed XRT, No. (%)	
No	1 (1.0)
Yes	95 (99.0)

Abbreviations: MDA, MD Anderson Cancer Center; UAE, United Arab Emirates; STR, subtotal resection; GTR, gross total resection; XRT, radiation therapy.

Seventeen patients (18%) were from outside the United States; 19 patients (20%) were from Houston, Texas; 21 (22%) were from other cities inside Texas; and 39 (41%) were from other US states. Thus, 42% (n = 40) of the treated patients were considered local (within Texas), whereas most patients (n = 56; 58%) traveled from afar. The median patient travel distance to MDA was 1622 km (1008 miles; range, 1-9362). The median time from surgery to start of radiation was 1.22 months (range, 0.6-45.2), and the median time from diagnosis to surgery was 2 days (0-642). Travel distance by international status and by state is presented pictorially in **Figures 1** and **2**.

When evaluating time to treatment start based on location, the median time from surgery to start of radiation was 1.45 months for patients outside the United States and 1.15 months for patients in the United States, with no statistically significant differences between groups ($P = .13$; 95% CI, –0.09 to 0.66). Furthermore, the median time from surgery to the start of radiation was 1.18 months for patients in Texas and 1.14 months for patients in other US states, with no statistically significant differences between groups ($P = .32$; 95% CI, –0.33 to 0.13). Therefore, time from surgery to treatment start was not affected by international or non-Texas location status.

However, when a cutoff of ≤ 1716 km (≤ 1066 miles) versus > 1716 km (> 1066 miles) from our proton center, suggested by the CART analyses, was used, the time from surgery to start of radiation was significantly longer for patients residing > 1716 km (> 1066 miles) from MDA (median = 1.31 months) than for patients residing ≤ 1716 km (≤ 1066 miles) from MDA (median = 1.05 months; $P = .01$; 95% CI, –0.76 to –0.06; **Table 2**). Thus, living > 1716 km (> 1066 miles) away correlated with a treatment delay of 1 to 2 weeks (7.8 days). However, that delay did not lead to any significant effect on FFS; there was no statistically significant association between residing > 1716 km (> 1066 miles) from MDA versus those residing ≤ 1716 km (≤ 1066 miles; 3-year FFS, 66.34% for ≤ 1716 km [≤ 1066 miles] and 59.58% for > 1716 km [> 1066 miles]; hazard ratio [HR] = 1.34; 95% CI, 0.65-2.74; $P = .43$; **Figure 3**).

Discussion

This study examined the association between travel distance and delay in proton therapy treatment for pediatric patients with medulloblastoma. Although we found that international patients had no significant delays in treatment time, patients traveling

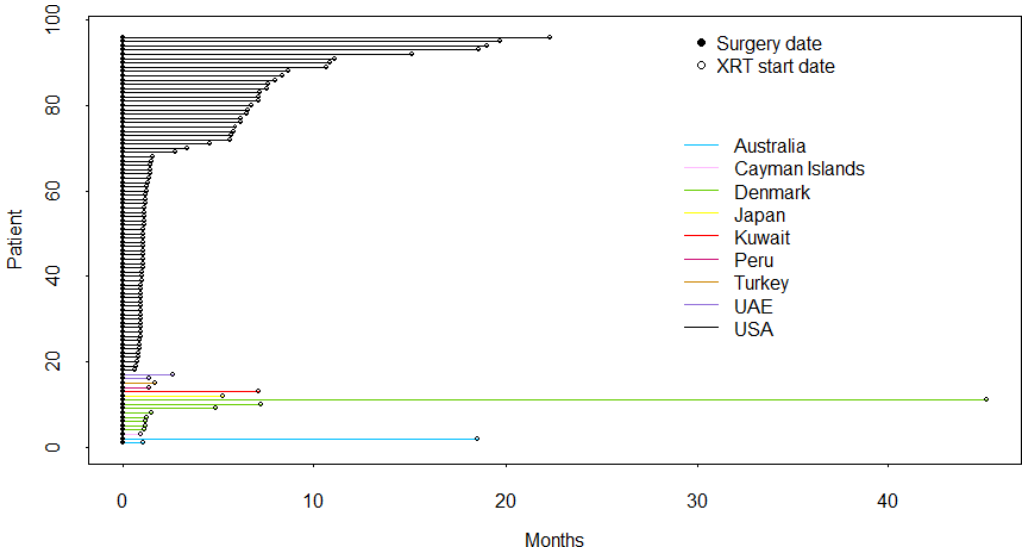


Figure 1. Event chart plot aligned by surgery date and sorted by country and time to start of radiation.

> 1716 km (> 1066 miles) to MDA had a 1- to 2-week delay (approximately 8 days) between surgery and treatment. However, that delay did not translate into worse outcomes for that group of patients. This highlights the appropriateness of seeking proton care in the face of travel coordination.

The importance of this study is in the context of the advantages of using proton therapy in the treatment of medulloblastoma. Medulloblastoma in children has generally consisted of a multidisciplinary approach of surgery, radiation therapy, and chemotherapy. One of the major problems of such an approach is the risk of long-term complications from traditional radiation therapy, which includes cognitive and adaptive functioning complications along with increased mortality secondary to heart disease [19–22]. Because of the risks associated with CSI and brain tumor treatment in children, physicians do not treat children younger than 3 years who have medulloblastoma and other brain tumors with radiation [23]. Proton therapy reduces the average radiation exposure during treatment of medulloblastoma, saving nearby structures from excess radiation and possibly affecting long-term sequelae [24, 25]. A recent study [26] showed favorable intellectual outcomes for patients with medulloblastoma treated with proton therapy compared with photon therapy, whereas others [27–30] have showed reduced late-toxicity risk, reduced chance of second malignancy, and reduced acute effects in patients with medulloblastoma who received proton therapy compared with those who did not. These studies show the safety and effectiveness of proton therapy in patients with medulloblastoma and continue to justify the preference of proton therapy for these children.

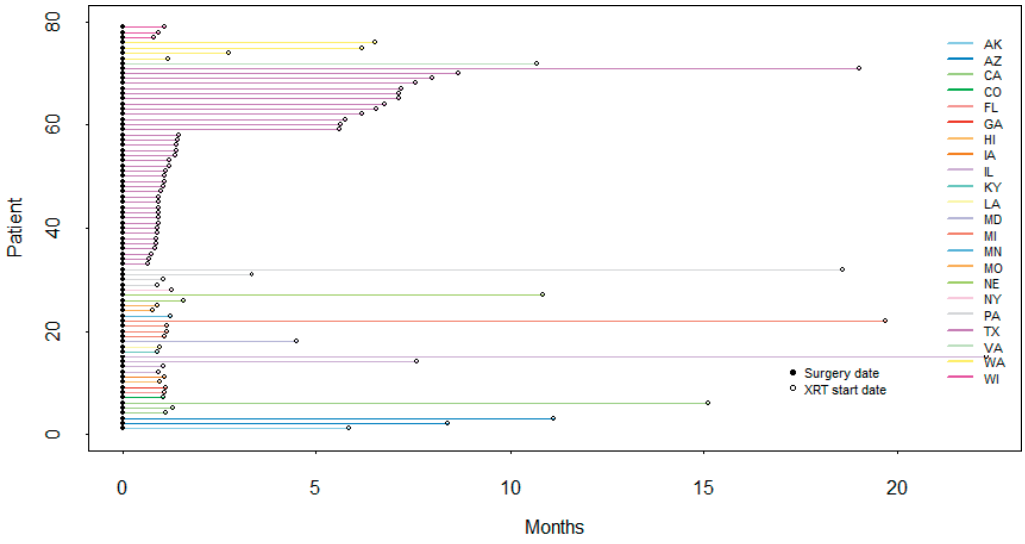


Figure 2. Event-chart plot aligned by surgery date and sorted by state and time to start of radiation.

Table 2. Association between distance from MD Anderson Cancer Center (MDA) and time from surgery to start of radiation.

Variable	Distance from MDA, km (miles)	Median	Minimum	Maximum	No. (%)	*P* value[a]	95% CI[b]
Time from surgery to start of radiation, mo	≤ 1716 km (≤ = 1066)	1.05	0.62	19.02	49 (51)	.012	−0.76 to 0.06
	> 1716 km (> 1066	1.31	0.79	45.17	47 (49)		
	Non-US patient	1.45	0.89	45.17	17 (18)	.129	−0.09 to 0.66
	US patient	1.15	0.62	22.31	79 (82)		

[a] Two-sided Wilcoxon rank-sum test.

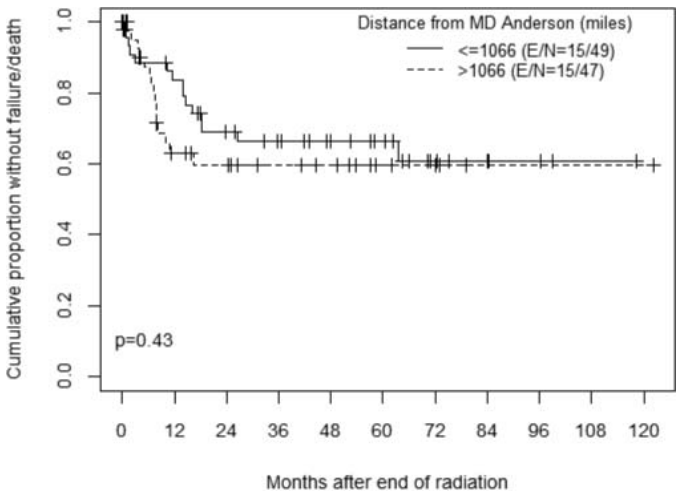
[a] Nonparametric 95% confidence interval (95% CI) for the difference in location.

Because proton therapy can reduce radiation exposure of surrounding healthy tissues in cancer treatment, its use has significantly increased in recent years [31]. This pattern is reflected in the increasing number of proton centers available in both the United States and internationally. There are currently 36 centers in operation in the United States and 69 centers operating internationally, with an additional 12 centers in the United States and 54 centers internationally under construction or in development [14]. In the United States, more than one-half (61%) of operating proton centers were opened within the past 5 years. Despite that increase, many patients have to travel significant distances to the nearest proton center to receive treatment. In our study, 58% (n = 56) of the patients traveled from outside of the state to receive treatment, including 18% (n = 17) of the patients traveling from outside the United States.

This is important in the context of medulloblastoma treatment because of correlations between travel distance and delays in treatment. Previous studies examining delays in adjuvant radiation therapy (including photon and proton radiotherapy) in patients with medulloblastoma have found conflicting results. One study found that delays greater than 5 weeks were not associated with inferior outcomes, while another found that delays greater than 3 months were associated with inferior outcomes [32, 33]. These studies may suggest that treatment delays in patients with medulloblastoma are a legitimate concern. Additional studies [34–37] that have examined the effect of delays in adjuvant chemotherapy and radiotherapy in various other malignancies, such as breast, early stage glottic, and other head and neck cancers, show that increasing time between diagnosis and treatment is associated with worse survival. Conversely, there was no association found between delay in treatment and relapse in other tumor types, such as acute lymphoblastic leukemia [38]. The effects of treatment delays on survival may be dependent on the type of cancer because rapidly progressive tumors will likely have more-adverse outcomes from delays compared with slowly growing tumors. Medulloblastomas grow relatively quickly, with symptoms and clinical presentation advancing within a period of weeks to months [39]. Therefore, even a short delay in treatment may adversely affect patient outcomes because the tumor has the potential to repopulate and attenuate subsequent treatment success.

The factors affecting the results of our study are likely multifaceted. International patients often come directly to MDA for treatment through agreements and relationships that MDA has established with international partners. Through that process, patients have a relatively streamlined process from diagnosis to treatment through a multifactorial team. On the other hand, patients who self-refer, often within the United States but outside of Texas, face more obstacles. The delay that these patients

Figure 3. Kaplan-Meier curves for failure-free survival by distance from MD Anderson Cancer Center.



experience is likely related to both socioeconomic factors and center-related and possibly payer-related variables such as prior authorization. When patients with medulloblastoma decide to receive proton therapy, the decision often occurs after the initial surgery and definitive diagnosis. There has to be a discussion between the patient and the provider, with time taken to decide whether proton therapy should be pursued and where to receive that therapy. Subsequently, it takes time to organize travel, refer to a proton center, and complete the intake process, which includes chart reviews, imaging reviews, as well as radiation treatment consultation. One additional factor affecting timeliness is dependence on prior authorization through insurance companies. A significant disparity in PBT coverage upon initial request when comparing Medicaid with private insurance companies (91% versus 30%) has been found, with a median time to approval of 21 days after an initial denial [40] for private insurance companies. In pediatric patients, coverage for PBT is denied in 11% of initial requests, but $>$ 99% of cases are ultimately approved [41]. This poses a potential barrier for patients with medulloblastoma who are often already burdened with delays because of travel to treatment centers.

Notably, and importantly, we found no association between a short 1- to 2-week delay in treatment and worse cancer outcomes for patients coming $>$ 1716 km ($>$ 1066 miles) from our center (3-year FFS approximately 60%, independent of distance; $P = .43$; **Figure 3**). Thus, patient access was successfully achieved without compromise in care. However, our results do shed light on the importance of a robust, streamlined intake process at proton centers to counter delays in treatment that may otherwise be out of the provider's hands. This is particularly relevant for proton centers with large volumes of patients coming from out of state (nearly 60% [n = 56; 58%] of all patients with medulloblastoma in this study at our center came from afar). At MDA, the current infrastructure of our intake process includes a team of multiple providers before, during, and after patient treatment. Initially, intake specialists receive patient-referral, process demographic, and insurance information. Patient-access specialists then authorize a consult appointment and verify authorization and benefits. Next, navigators gather pertinent imaging, pathology, and additional health record information. This allows for a provider to review the patient's information and approve an official scheduled consult. In coordination with a streamlined referral process as seen with the international patients, this has been shown to be effective at minimizing time between diagnosis and treatment, suggesting that a rigorous intake process is critical for proton centers to reduce delays that may adversely affect patient outcomes, including those of children [42]. Based on the results of our study, pediatric PBT patients living $>$ 1609 km ($>$ 1000 miles) away should be flagged and receive special attention by the intake team to prevent delays in treatment, which includes vigilant attention to payer authorization, travel navigation, and timely referral to social work or other team members equipped to assist families with expediting access.

Although these results are encouraging, we recognize the various limitations to our study. The small sample size and small number of international patients limit the ability to extrapolate our data. The size also limited our ability to do further advanced multivariate analyses to evaluate other factors that could have contributed to delays (eg, patient family income, demographic factors, parental education, referring practice status, and others). This may be an important next step in future research because identification of these factors in accordance with distance could affect referral and treatment decisions. Lastly, we also recognize that because of the retrospective nature of our study, the research and data we present here are hypothesis generating, and the small sample size requires validation of our results by other centers with larger numbers of patients.

Conclusions

Patients receiving proton therapy can experience delays in treatment based on access to proton centers within local proximity. Although we found that an established referral process for international patients led to no delays in treatment, patients traveling $>$ 1716 km ($>$ 1066 miles) had a 1- to 2-week (approximately 8 day) delay. However, this minor delay was not associated with worse results, and patient access was preserved. Thus, traveling to a proton center to receive high-quality care—even across country—does not compromise outcomes and is important for providers and parents to recognize as they seek best-care practices for their children. Our findings highlight the importance of a streamlined referral intake process to prevent undue delays and to continue avoiding potential compromises in outcomes because of the referral nature to proton centers across the globe.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Steven J. Frank, MD, is an Associate Editor of the *International Journal of Particle Therapy*. Dr Frank discloses leadership and ownership interests in C4 Imaging and National Comprehensive Cancer Network Stock; honoraria

from Boston Scientific, Hitachi, and Varian Medical Systems; research funding from Elekta, Hitachi, and Eli Lilly; a consulting or advisory role with Hitachi, Breakthrough Chronic Care, Varian Medical Systems; and patents developed at the University of Texas MD Anderson Cancer Center, which have been licensed to C4 Imaging. Dr Frank also discloses travel, accommodations, and expenses provided by the National Comprehensive Cancer Network and Boston Scientific. The authors have no other conflicts to disclose.

Funding: The authors have no additional funding to disclose.

Ethical Approval: All patient data has been collected under internal review board–approved protocol.

Consortium: The MD Anderson Cancer Center Radiation Oncology Fellows Consortium included the following members: Brandon Lucari, Saira Elizabeth Alex, Carolyn Brooks, Karthik Jagannath, Rohit Gupta, Bethany Burdick, Alexandria Brown, and Lorna Min.

References

1. Smoll NR, Drummond KJ. The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children. *J Clin Neurosci*. 2012;19:1541–4.
2. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. *Neuro Oncol*. 2018;20(suppl 4):iv1–86.
3. Jones DT, Jäger N, Kool M, Zichner T, Hutter B, Sultan M, Cho YJ, Pugh TJ, Hovestadt V, Stütz AM, Rausch T, Warnatz HJ, Ryzhova M, Bender S, Sturm D, Pleier S, Cin H, Pfaff E, Sieber L, Wittmann A, Remke M, Witt M, Hutter S, Tzaridis T, Weischenfeldt J, Raeder B, Avci M, Amstislavskiy V, Zapatka M, Weber UD, Wang Q, Lasitschka B, Bartholomae CC, Schmidt M, von Kalle C, Ast V, Lawerenz C, Eils J, Kabbe R, Benes V, van Sluis P, Koster J, Volckmann R, Shih D, Betts MJ, Russell RB, Coco S, Tonini GP, Schüller U, Hans V, Graf N, Kim YJ, Monoranu C, Roggendorf W, Unterberg A, Herold-Mende C, Milde T, Kulozik AE, von Deimling A, Witt O, Maass E, Rössler E, Ebinger M, Schuhmann MU, Frühwald MC, Hasselblatt M, Jabado N, Rutkowski S, O von Bueren A, Williamson D, Clifford SC, McCabe MG, Collins VP, Wolf S, Wiemann S, Lehrach H, Brors B, Scheurlen A, Felsberg J, Reifenberger G, Northcott PA, Taylor MD, Meyerson M, Pomeroy SL, Yaspo ML, Korbel JO, Korshunov A, Eils R, Pfister SM, Lichter P. Dissecting the genomic complexity underlying medulloblastoma. *Nature*. 2012;488:100–5.
4. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, Ellison DW, Lichter P, Gilbertson RJ, Pomeroy SL, Kool M, Pfister SM. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol*. 2012;123:465–72.
5. St Clair WH, Adams JA, Bues M, Fullerton BC, La Shell S, Kooy HM, Loeffler JS, Tarbell NJ. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2004;58:727–34.
6. Kahalley LS, Peterson R, Ris MD, Janzen L, Okcu MF, Grosshans DR, Ramaswamy V, Paulino AC, Hodgson D, Mahajan A, Tsang DS, Laperriere N, Whitehead WE, Dauser RC, Taylor MD, Conklin HM, Chintagumpala M, Bouffet E, Mabbott D. Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. *J Clin Oncol*. 2020;38:454–61.
7. Yuh GE, Loredo LN, Yonemoto LT, Bush DA, Shahnazi K, Preston W, Slater JM, Slater JD. Reducing toxicity from craniospinal irradiation: using proton beams to treat medulloblastoma in young children. *Cancer J*. 2004;10:386–90.
8. Paulino AC, Mahajan A, Ye R, Grosshans DR, Okcu MF, Su J, McAleer MF, McGovern S, Mangona VA, Chintagumpala M. Ototoxicity and cochlear sparing in children with medulloblastoma: proton vs. photon radiotherapy. *Radiother Oncol*. 2018;128:128–32.
9. Yock TI, Yeap BY, Ebb DH, Weyman E, Eaton BR, Sherry NA, Jones RM, MacDonald SM, Pulsifer MB, Lavally B, Abrams AN, Huang MS, Marcus KJ, Tarbell NJ. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study [published correction appears in *Lancet Oncol.* 2020;21:e132]. *Lancet Oncol.* 2016;17:287–98.
10. Fossati P, Ricardi U, Orecchia R. Pediatric medulloblastoma: toxicity of current treatment and potential role of protontherapy. *Cancer Treat Rev*. 2009;35:79–96.
11. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, Hamilton W, Hendry A, Hendry M, Lewis R, Macleod U, Mitchell ED, Pickett M, Rai T, Shaw K, Stuart N, Tørring ML, Wilkinson C, Williams B, Williams N, Emery J. Is

increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? systematic review. *Br J Cancer*. 2015;112(suppl 1):S92–107.

12. Hershman DL, Wang X, McBride R, Jacobson JS, Grann VR, Neugut AI. Delay in initiating adjuvant radiotherapy following breast conservation surgery and its impact on survival. *Int J Radiat Oncol Biol Phys*. 2006;65(5):1353–60.
13. Paulino AC, Jaboin JJ. Radiotherapy deferral in medulloblastoma. *JAMA Oncol*. 2016;2:1582.
14. Particle Therapy Co-Operative Group. Particle therapy facilities in clinical operation. https://www.ptcog.ch/index.php/facilities-in-operation. Published 2020. Accessed June 28, 2020.
15. Adler JT, Bababekov YJ, Markmann JF, Chang DC, Yeh H. Distance is associated with mortality on the waitlist in pediatric liver transplantation. *Pediatr Transplant*. 2017;21. doi: 10.1111/petr.12842.
16. McKane M, Dodd DA, Mettler BA, Wujcik KA, Godown J. Geographic distance from transplant center does not impact pediatric heart transplant outcomes. *Prog Transplant*. 2018;28:170–3.
17. Kelly C, Hulme C, Farragher T, Clarke G. Are differences in travel time or distance to healthcare for adults in global north countries associated with an impact on health outcomes? a systematic review. *BMJ Open*. 2016;6:e013059.
18. Breiman L, Friedman JH, Olshen RA and Stone CJ. *Classification and Regression Trees*. Boca Raton, FL: Chapman & Hall/CRC; 1984.
19. de Ruiter MA, van Mourik R, Schouten-van Meeteren AY, Grootenhuis MA, Oosterlaan J. Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis. *Dev Med Child Neurol*. 2013;55:408–17.
20. Merchant TE, Kiehna EN, Li C, Xiong X, Mulhern RK. Radiation dosimetry predicts IQ after conformal radiation therapy in pediatric patients with localized ependymoma. *Int J Radiat Oncol Biol Phys*. 2005;63:1546–54.
21. Ashford JM, Netson KL, Clark KN, Merchant TE, Santana VM, Wu S, Conklin HM. Adaptive functioning of childhood brain tumor survivors following conformal radiation therapy. *J Neurooncol*. 2014;118:193–9.
22. Mulhern RK, Palmer SL, Merchant TE, Wallace D, Kocak M, Brouwers P, Krull K, Chintagumpala M, Stargatt R, Ashley DM, Tyc VL, Kun L, Boyett J, Gajjar A. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. *J Clin Oncol*. 2005;23:5511–9.
23. De Luca CR, Conroy R, McCarthy MC, Anderson VA, Ashley DM. Neuropsychological impact of treatment of brain tumors. *Cancer Treat Res*. 2009;150:277–96.
24. Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer*. 2008;51:110–7.
25. Hoffman KE, Yock TI. Radiation therapy for pediatric central nervous system tumors. *J Child Neurol*. 2009;24:1387–96.
26. Kahalley LS, Peterson R, Ris MD, Janzen L, Okcu MF, Grosshans DR, Ramaswamy V, Paulino AC, Hodgson D, Mahajan A, Tsang DS, Laperriere N, Whitehead WE, Dauser RC, Taylor MD, Conklin HM, Chintagumpala M, Bouffet E, Mabbott D. Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. *J Clin Oncol*. 2020;38:454–61.
27. Grewal AS, Li Y, Fisher MJ, Minturn J, Paltin I, Belasco J, Phillips P, Kang T, Lustig RA, Hill-Kayser C. Tumor bed proton irradiation in young children with localized medulloblastoma. *Pediatr Blood Cancer*. 2019;66:e27972.
28. Mu X, Björk-Eriksson T, Nill S, Oelfke U, Johansson KA, Gagliardi G, Johansson L, Karlsson M, Zackrisson B. Does electron and proton therapy reduce the risk of radiation induced cancer after spinal irradiation for childhood medulloblastoma? a comparative treatment planning study. *Acta Oncol*. 2005;44:554–62.
29. Brown AP, Barney CL, Grosshans DR, McAleer MF, de Groot JF, Puduvalli VK, Tucker SL, Crawford CN, Khan M, Khatua S, Gilbert MR, Brown PD, Mahajan A. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2013;86:277–84.
30. Brodin NP, Munck Af Rosenschöld P, Aznar MC, Aznar MC, Kiil-Berthelsen A, Vogelius IR, Nilsson P, Lannering B, Björk-Eriksson T. Radiobiological risk estimates of adverse events and secondary cancer for proton and photon radiation therapy of pediatric medulloblastoma. *Acta Oncol*. 2011;50:806–16.
31. Odei B, Frandsen JE, Boothe D, Ermoian RP, Poppe MM. Patterns of care in proton radiation therapy for pediatric central nervous system malignancies. *Int J Radiat Oncol Biol Phys*. 2017;97:60–3.

32. Chin AL, Moding EJ, Donaldson SS, Gibbs IC, Soltys SG, Hiniker SM, Pollom EL. Survival impact of postoperative radiotherapy timing in pediatric and adolescent medulloblastoma. *Neuro Oncol*. 2018;20:1133–41.
33. Kann BH, Park HS, Lester-Coll NH, Yeboa DN, Benitez V, Khan AJ, Bindra RS, Marks AM, Roberts KB. Postoperative radiotherapy patterns of care and survival implications for medulloblastoma in young children [published correction appears in *JAMA Oncol.* 2016;2:1661].*JAMA Oncol.* 2016;2(12):1574–81.
34. Karlsson P, Cole BF, Price KN, Gelber RD, Coates AS, Goldhirsch A, Castiglione M, Colleoni M, Gruber G; International Breast Cancer Study Group. Timing of radiation therapy and chemotherapy after breast-conserving surgery for node-positive breast cancer: long-term results from International Breast Cancer Study Group Trials VI and VII. *Int J Radiat Oncol Biol Phys*. 2016;96:273–9.
35. Khorana AA, Tullio K, Elson P, Pennell NA, Grobmyer SR, Kalady MF, Raymond D, Abraham J, Klein EA, Walsh RM, Monteleone EE, Wei W, Hobbs B, Bolwell BJ. Time to initial cancer treatment in the United States and association with survival over time: an observational study [published correction appears in *PLoS One*. 2019;14:e0215108]. *PLoS One*. 2019;14:e0213209.
36. Cheraghlou S, Kuo P, Judson BL. Treatment delay and facility case volume are associated with survival in early-stage glottic cancer. *Laryngoscope*. 2017;127(3):616–22.
37. Coca-Pelaz A, Takes RP, Hutcheson K, Saba NF, Haigentz M Jr, Bradford CR, de Bree R, Strojan P, Lund VJ, Mendenhall WM, Nixon IJ, Quer M, Rinaldo A, Ferlito A. Head and neck cancer: a review of the impact of treatment delay on outcome. *Adv Ther*. 2018;35:153–60.
38. Yeoh A, Collins A, Fox K, Shields S, Ritchie P, Kirby M, Revesz T. Treatment delay and the risk of relapse in pediatric acute lymphoblastic leukemia. *Pediatr Hematol Oncol*. 2017;34:38–42.
39. Millard NE, De Braganca KC. Medulloblastoma [published correction appears in *J Child Neurol.* 2016; 0883073816670445]. *J Child Neurol.* 2016;31:1341–53.
40. Ning MS, Gomez DR, Shah AK, Kim CR, Palmer MB, Thaker NG, Grosshans DR, Liao Z, Chapman BV, Brooks ED, Tang C, Rosenthal DI, Garden AS, Frank SJ, Gunn GB. The insurance approval process for proton radiation therapy: a significant barrier to patient care. *Int J Radiat Oncol Biol Phys*. 2019;104:724–33.
41. Ojerholm E, Hill-Kayser CE. Insurance coverage decisions for pediatric proton therapy. *Pediatr Blood Cancer*. 2018;65. doi: 10.1002/pbc.26729.
42. Common JL, Mariathas HH, Parsons K, Greenland JD, Harris S, Bhatia R, Byrne SC. Reducing wait time for lung cancer diagnosis and treatment: impact of a multidisciplinary, centralized referral program. *Can Assoc Radiol J*. 2018;69:322–7.