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Medulloblastoma

Treatment outcome and prognostic factors for adult patients with medulloblastoma: The Rare Cancer Network (RCN) experience ☆

Banu Atalar [a,2], Mahmut Ozsahin [b], Jason Call [n,1], Aleksandra Napieralska [c], Serra Kamer [d], Salvador Villa [e], Petek Erpolat [f], Laura Negretti [b], Yasmin Lassen-Ramshad [g], Cem Onal [h], Serap Akyurek [i], Gamze Ugurluer [a], Brigitta G. Baumert [j,k], Stephanie Servagi-Vernat [l], Robert C. Miller [m], Enis Ozyar [a,2], Terence T. Sio [n,*]

[a] Department of Radiation Oncology, Acıbadem University, Istanbul, Turkey; [b] Centre Hospitalier Universitaire Vaudois (CHUV), Department of Radiation Oncology, Lausanne, Switzerland; [c] Radiotherapy Department, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland; [d] Department of Radiation Oncology, Ege University, Izmir, Turkey; [e] Radiation Oncology, Catalan Institute of Oncology, Badalona, Catalonia, Spain; [f] Department of Radiation Oncology, Gazi University, Ankara, Turkey; [g] Oncological Department, Aarhus University Hospital, Denmark; [h] Department of Radiation Oncology, Baskent University, Adana; [i] Department of Radiation Oncology, Ankara University, Ankara, Turkey; [j] Depts. Radiation Oncology (MAASTRO), GROW, Maastricht University MC, Netherlands; [k] Paracelsus Klinik Osnabrueck and University of Muenster, University Bonn MC, Germany; [l] Radiation Oncology, University Hospital of Besancon, France; [m] Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL; and [n] Department of Radiation Oncology, Mayo Clinic Hospital, Phoenix, AZ, United States

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ABSTRACT

Background and purpose: The optimal treatment for adults with newly diagnosed medulloblastoma (MB) has not been defined. We report a large series of cases from the Rare Cancer Network.

Material and methods: Thirteen institutions enrolled 206 MB patients who underwent postoperative radiotherapy (RT) between 1976 and 2014. Log-rank univariate and Cox-modeled multivariate analyses were used to analyze data collected.

Results: Median patient age was 29 years; follow-up was 31 months. All patients had the tumor resected; surgery was complete in 140 (68%) patients. Postoperative RT was given in 202 (98%) patients, and 94% received craniospinal irradiation (CSI) and, usually, a posterior fossa boost. Ninety-eight (48%) patients had chemotherapy, mostly cisplatin and vincristine-based. The 10-year local control, overall survival, and disease-free survival rates were 46%, 51%, and 38%, respectively. In multivariate analyses, Karnofsky Performance Status (KPS) $\geq$80 and CSI were significant for disease-free and overall survival ($P \leq .04$ for all); receiving chemotherapy and KPS $\geq$80 correlated with better local-control rates.

Conclusions: Patients with high KPS who received CSI had better rates of disease-free and overall survival. Chemotherapy was associated with better local control. These results may serve as a benchmark for future studies designed to improve outcomes for adults with medulloblastoma.

Medulloblastoma (MB) is the most common brain tumor in children and is typically cerebellar in origin. However, it is extremely rare in adults, accounting for less than 1% of adult craniospinal tumors, with an incidence of about 0.6–1 case per million [1,2]. The treatment of pediatric MBs has been reported for prospective studies, and prognostic factors and therapeutic guidelines are well-defined [3–5]. However, reports of adults with MBs are limited to retrospective series of single-institution trials, and the role of chemotherapy (CT) in treatment has been controversial [6–8].

In the early 1990s, the Rare Cancer Network (RCN) was formed to allow investigators throughout the world to combine data and share resources to enhance the study of malignant tumors that cannot be studied in prospective trials because of their rarity (http://www.rarecancer.net). To date, 90 studies have been completed and 54 peer-reviewed manuscripts published, mainly multiinstitutional retrospective analyses [9–12]. Within this context,

Abbreviations: CSI, craniospinal irradiation; CT, chemotherapy; KPS, Karnofsky Performance Status; MB, medulloblastoma; RCN, Rare Cancer Network; RT, radiotherapy; SHH, sonic hedgehog; SRS, stereotactic radiosurgery; WNT, wingless.

☆ The results of this work have been presented in part as an oral presentation at the ESTRO 35 conference in Turin, Italy, held April 29 to May 3, 2016; the abstract was also selected as one of five for the ESTRO 35 Congress Report/Top Abstracts by chairs of the clinical track.

* Corresponding author at: Department of Radiation Oncology, Mayo Clinic Hospital, Phoenix, AZ, United States.

E-mail address: banu.atalar@acibadem.com.tr (B. Atalar).

[1] Present address: Cancer Care Northwest, North Spokane, Spokane, WA, United States.

[2] Department of Radiation Oncology, Acibadem University, School of Medicine, Acibadem Maslak Hospital, Maslak, 34457 Istanbul, Turkey.

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the RCN study group decided on an international collaborative effort to report the common treatment paradigm for adult patients affected by MB and to determine clinical outcomes and prognostic factors. On behalf of RCN, we report the clinical outcomes of a retrospective study of this multiinstitutional cohort of adult patients treated with postoperative radiotherapy (RT) and CT; toxicity analyses were not included.

Material and methods

All contributors received approval from their respective institutional review boards at individual hospitals. A proposal describing the suggested project and research plan was sent to the RCN headquarters. Those who agreed to participate sent their patients' clinical data, including the associated prognostic factors and survival outcomes, to the primary investigators. To be included, patients had to be 16 years or older (age 16 was considered as adult at the participating institutions), with histologic findings (any subtype) confirmed by their local institution from 1976 to 2014. There was no exclusion for therapeutic approach as long as the intent was not palliative. All patient data, including demographic and clinical information, were collected through retrospective review of written and electronic health records.

The data collection and evaluation were completed in early 2016. Extracted data were sent to one investigator (B.A.) for data analyses and statistical summaries. All patients were included in the final analyses.

Statistical analysis

Overall survival, disease-free survival, and actuarial locoregional and local control rates were calculated using the product-limit and Kaplan–Meier methods [13]. Time to any event was measured from the date of pathologic diagnosis, which was the date of surgery or biopsy (if the tumor was inoperable). Overall survival was defined as the time period for which the patient was recorded to be alive, or last follow-up. Disease-free survival was defined as the time period for which the patient was alive and recurrence-free, or last follow-up. Locoregional recurrence was defined as an event consisting of local or regional relapse (local relapse for local control). Patients without relapse were censored at their last follow-up. Differences between groups were assessed using the log-rank test [14]. Multivariate analyses were done using the Cox stepwise-regression analysis to determine the independent contribution of each prognostic factor [15]. Disease and treatment characteristics evaluated as univariate parameters were not counted if they were not reported by the contributing institutions (for that particular factor only). Toxicity was not evaluated because of the diversity of therapies and RT doses and also because of the heterogeneity of electronic medical records and evaluation systems among the different hospitals providing data.

Results

Between 1976 and 2014, 206 adult patients with MB were identified from 13 institutions in Europe and the United States. One hospital contributed 66 (32%) of the patient cases (J.C., R.C.M., and T.T.S.).

Patient and tumor characteristics

Patient and tumor characteristics are shown in Table 1. The median (range) age of the cohort was 29 (16–66) years, and there were more men (57%). At diagnosis, 2 patients were 16 years, and 10 patients were 17 years. The Karnofsky Performance Status (KPS) score was 80 or more in 53% of the patients. The pathologic subtype was classic in 61%, desmoplastic in 25%, and other subtypes or unknown in the remainder of patients. Of all patients, 74% had T1–T2 stage tumors, and 26% had T3 stage tumors. Evidence of tumor seeding was seen on magnetic resonance imaging in 14 patients, and craniospinal fluid evaluation was done in 154 (75%) patients; 12 patients had positive findings by cytology. Most of our patients did not have spinal metastatic deposits from MB at diagnosis.

Table 1
Patient and Tumor Characteristics.

Characteristic	No. (%)[a] (*N* = 206)
Age, median (range), y	29 (16–66)
Sex, male	118 (57)
Karnofsky Performance Status score	
≥80	110 (53)
<80	27 (13)
Unknown	69 (33)
Pathologic subtype	
Classic	125 (61)
Desmoplastic	52 (25)
Other types	14 (7)
Unknown	15 (7)
T stage	
T1	12 (12)
T2	62 (62)
T3a	18 (18)
T3b	8 (8)
Not reported	106[b]
M stage	
M0	34 (62)
M1	9 (16)
M2	9 (16)
M3	3 (5)
Not reported	151[b]
MRI evidence of spinal seeding	
Yes	14 (7)
No	192 (93)
Positive findings, craniospinal fluid	
Yes	12 (6)
No	142 (69)
Unknown	52 (25)

Abbreviation: MRI, magnetic resonance imaging.
[a] May not add to 100% because of rounding.
[b] Not counted in variate analyses; therefore, not reported as percentages.

Patients had tumors in 57 sites in the brain: 32 patients had 4th ventricular floor involvement; 11, peduncular involvement; 2, both 4th ventricular and peduncular involvement; 7, brainstem invasion; 2, posterior cerebellar artery; 1, other cerebellar lobe; 1, extra-axial tentorial; and 1, vermis. Locations of spinal metastases were known for 7 of 14 patients: 1, cervical; 1, cervical/thoracic; 2, cervical/lumbar; 1, cervical/thoracic/lumbar; and 2, sacrum.

Treatment characteristics

All patients underwent an initial neurosurgical procedure (Table 2). Of the patients, 68% had a complete surgery; 27%, incomplete surgery; and 4%, an inoperable tumor or biopsy, or both. After surgery, 61% of patients had residual tumors, which were less than 1.5 cm^2 in 66% of the patients. The median (range) time between surgery and RT was 47 (9–210) days.

Treatment of MB with RT and CT varied because of geographic and institutional practice differences. Most patients (94%) were treated with craniospinal irradiation (CSI) and a boost dose to the posterior fossa (92%); however, 13 patients did not have CSI, and 16 did not receive a boost (Table 2). Three (1%) patients

Table 2
Treatment Characteristics for Adult Patients With Medulloblastoma.

Treatment	No. (%)[a,b] (*N* = 206)
Surgery	
Complete resection	140 (68)
Incomplete resection	56 (27)
Inoperable	9 (4)
Not reported	1[c]
Residual tumor extent	
≤1.5 cm^2	83 (66)
>1.5 cm^2	42 (34)
Not reported	81[c]
Surgery to RT duration	
Mean (SD), d	61 (44)
Median (quartiles), d	47 (28–90)
Not reported	69[c]
Use of CSI	
Received CSI	193 (94)
No CSI	13 (6)
CSI RT dose	
Mean (SD), Gy	32 (11)
Median (quartiles), Gy	36 (23–36)
Received RT boost	
Yes	190 (92)
No	16 (8)
Boost RT dose	
Mean (SD), Gy	17 (8)
Median (quartiles), Gy	18 (16–20)
Total RT dose to posterior fossa	
Mean (SD), Gy	54 (7)
Median (quartiles), Gy	54 (54–55.8)
Received adjuvant CT	
Yes	98 (48)
No	108 (52)
Timing of adjuvant CT	
After RT	33 (37)
Before RT	29 (32)
Before/concurrent/after RT	2 (2)
Concurrent/after RT	12 (13)
Concurrent with RT	14 (16)
Not reported	8[d]

Abbreviations: CSI, craniospinal irradiation; CT, chemotherapy; RT, radiotherapy.
[a] May not add to 100% due to rounding.
[b] No. (%) unless otherwise indicated.
[c] Not counted in variate analyses; therefore, not reported as percentages.
[d] This factor was not included in any variate analyses; the "not reported" category was not included in percentages.

received local RT (without CSI). The median (range) CSI dose was 36 (23.0–50.0) Gy; the median (range) boost dose to the posterior fossa was 18 (16.0–34.2) Gy, with a median (range) RT fraction size of 1.8 (1.5–2.0) Gy. The total RT dose for the posterior fossa was a median (range) of 54 (35.2–72.0) Gy. Adjuvant CT (before, concomitant, or after RT) was used for 98 patients (48%); of these, 37% received CT after RT, 32% before RT, and 31% concurrent with RT or continued after RT, or both. Over the years, the CT regimens varied, but the most common agents were vincristine and cisplatin-based therapies. Carboplatin, lomustine, and cyclophosphamide-containing regimens were also used. For 61 patients with reported durations of CT, 33 (54%) received 6 or 8 cycles. Intrathecal CT was rarely used (1 case).

Disease and patient outcomes

The median (range) follow-up was 31 (0.2–179) months (quartiles, 12–75 months). During follow-up, 45 patients died of disease, 22 died of intercurrent disease, 125 were alive without evidence of disease, 12 were alive with disease, and 2 were lost to follow-up.

Tumors recurred locally in 57 patients: in the brain, 43 patients; spine, 5 patients; and brain and spine, 9 patients. Metastatic disease occurred in 7 patients (bone, bone marrow, intraperitoneal cavity, and intramuscular sites). The salvage methods were individualized and included no further treatment/best supportive care (6 patients); CT and surgery (13 patients); CT alone (12 patients); RT alone, including stereotactic radiosurgery (SRS) (7 patients); surgery alone (9 patients); CT and RT, including SRS (9 patients); and other methods (3 patients) (59 cases [92% of 64 recurrences] reported with information about salvage therapy). Fractionated high-dose stereotactic RT was also used and included in the SRS counts. The local-control rates were 60% and 46%, respectively (Fig. 1A) for all patients, and disease-free survival rates were 52% and 38% at 5 and 10 years (Fig. 1B). At 5 years, the overall survival rate was 63%; at 10 years, it was 51% (Fig. 1C).

Outcomes by univariate analyses

On univariate analyses, a KPS score of 80 or more, time between surgery and RT (≤47 days), negative CSF results by cytology, total RT dose to the posterior fossa of at least 54 Gy, CSI completion, use of an RT boost, and CT were associated with better local control, disease-free survival, and overall survival (Table 3). The relationship of adjuvant CT and CSI with local control and overall survival is shown in Fig. 2A–D. The favorable significant prognostic factors for disease-free survival and overall survival remained with a KPS score of at least 80 ($P < .001$) and CSI ($P < .001$) in multivariate analyses (Table 4). Additionally, our results also showed that CT ($P < .001$) and a KPS score of at least 80 ($P = .03$) correlated with better local control rates (Table 4). KPS greater than 80 and CSF negativity were significantly correlated with local control, disease-free survival, and overall survival ($P \leq .04$ for all).

On univariate analysis, age less than 29 years and a residual volume less than 1.5 cm^2 after surgery correlated with better disease-free survival and overall survival. Desmoplastic pathologic findings were shown to be a favorable prognostic factor for disease-free survival. The following treatment-related factors were favorable prognostically for local control, disease-free survival, and overall survival: more than 47 days between surgery and RT, total RT dose to the posterior fossa of at least 54 Gy, a CSI boost to the posterior fossa, and adjuvant CT ($P \leq .04$ for all).

Outcomes by multivariate analyses

On multivariate analysis, the KPS score remained significant as a favorable factor for local control, disease-free survival, and overall survival ($P \leq 0.04$ for all). Patients treated with adjuvant CT had better local control, which was also reflected in improved survival ($P < .03$). Use of CSI was strongly, significantly correlated with improved disease-free and overall survivals ($P \leq .002$ for both).

Discussion

The cornerstone of treatment for adults with MB remains surgery, followed by RT-based regimens (with or without CT) because of high incidence of recurrence [16,17]. Delaying RT for more than 5 weeks has been shown to be a risk factor for local control and impaired prognosis [18]. Large, retrospective, single-institution series have provided information about prognostic risk factors and survival; however, controversy remains regarding the use of concurrent or adjuvant CT, or both [19–22]. To our knowledge, this study is the largest, multiinstitutional report about multimodality therapy approaches for treatment of adult MB.

Recently, a small, phase II prospective study by the ECOG-ACRIN Cancer Research Group [23] reported that 11 adult patients with high-risk MB received postoperative CT first, followed by CSI-

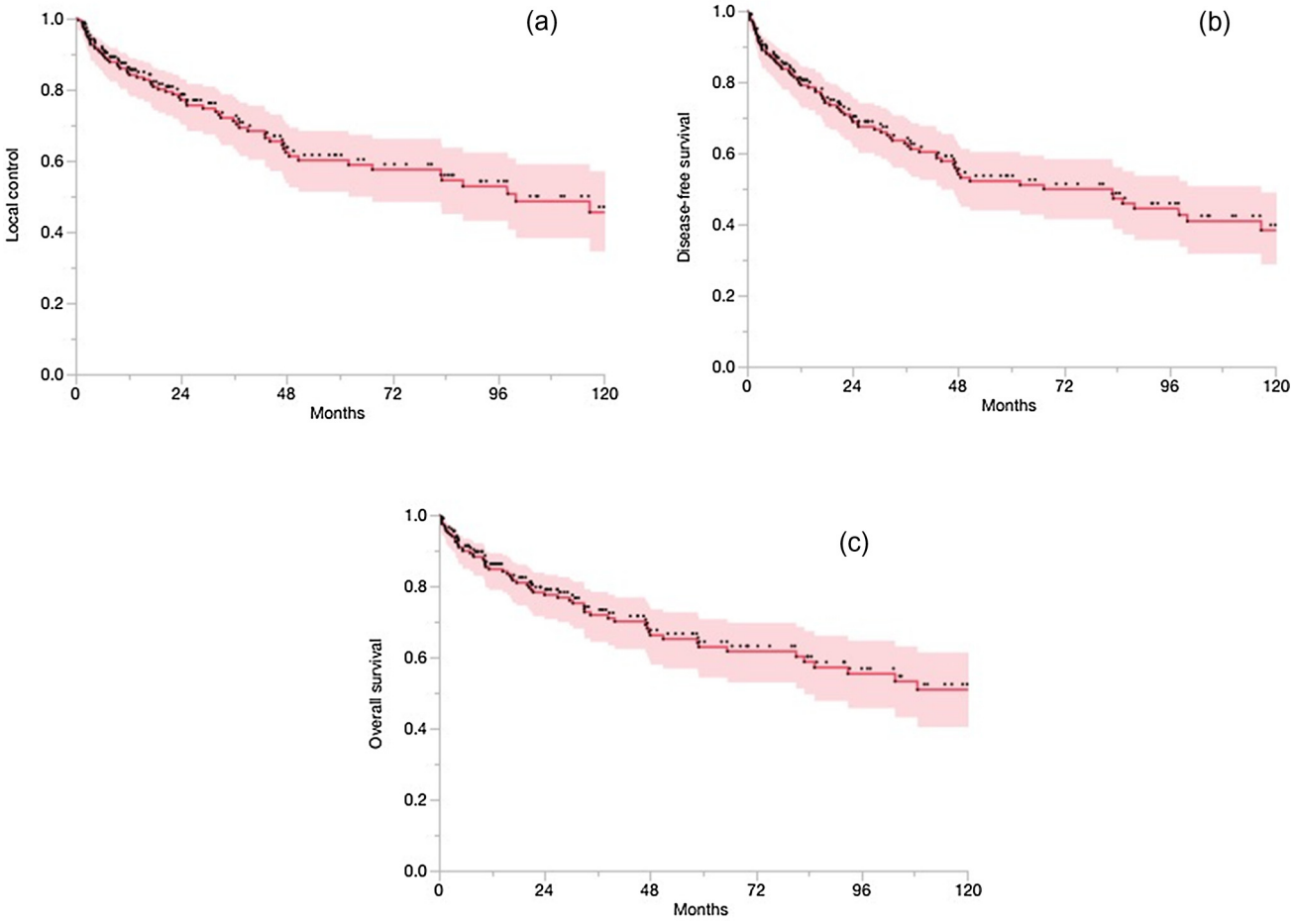

Fig. 1. Adult patients with medulloblastoma. (A) Local control. (B) Disease-free survival. (C) Overall survival.

Table 3
Statistical Results With Univariate Analysis.

Factors	Comparison	5-Year local control, %	*P* value	5-Year disease-free survival, %	*P* Value	5-Year overall survival, %	*P* value
Clinical factors							
Age, y	≤29 vs >29	68 vs 51	NS	63 vs 40	.03	76 vs 50	.004
KPS score	≥80 vs <80	72 vs 35	<.001	67 vs 22	<.001	79 vs 35	<.001
Sex	Female vs male	60 vs 59	NS	51 vs 52	NS	64 vs 62	NS
CSF involvement	Negative vs positive	63 vs 55	.03	55 vs 47	.02	67 vs 52	.04
Pathologic finding	Desmoplastic vs classic	74 vs 57	NS	71 vs 47	.03	77 vs 58	NS
Therapeutic factors							
Surgical extent	Complete resection vs other	63 vs 55	NS	56 vs 44	.02	66 vs 56	.01
Residual volume	≤1.5 cm^2 vs >1.5 cm^2	59 vs 63	NS	53 vs 45	.04	63 vs 51	.02
Spinal metastases by MRI	No vs yes	62 vs 39	NS	53 vs 38	NS	64 vs 53	NS
CSI RT	Yes vs no	61 vs 0	.002	55 vs 0	<.001	53 vs <14[a]	<.001
Time from surgery to RT, d	≤47 vs >47	56 vs 72	.03	53 vs 70	.04	67 vs 79	.03
Total RT dose to posterior fossa, Gy	<54 vs ≥54	12 vs 60	<.001	8 vs 65	<.001	25 vs 74	<.001
Use of RT boost	Yes vs no	62 vs 0	<.001	55 vs 0	<.001	66 vs <12[a]	<.001
Use of chemotherapy[b]	Yes vs no	74 vs 50	.03	65 vs 43	.02	73 vs 55	.03

Abbreviations: CSF, cerebrospinal fluid; CSI, craniospinal irradiation; KPS, Karnofsky Performance Status; MRI, magnetic resonance imaging; NS, not statistically significant; RT, radiotherapy.

[a] "53 vs 14 (%)" and "66 vs 12 (%)" are actuarial because of lack of data points in the "CSI RT" and "RT boost dose" groups at 5 years.

[b] Also includes neoadjuvant, concomitant, or adjuvant therapies.

based RT. The CT consisted of 3 cycles of cisplatin, etoposide, cyclophosphamide, and vincristine. However, in this small study, the objective response rate for pre-RT CT was lower than anticipated, and the benefits attained by the addition of CT were controversial. It appeared that pre-RT CT may actually have been harmful; the 5-year overall survival and progression-free survival rates were 55% and 27%, respectively, which was lower than that of 2 other series, which reported overall survival rates of 72% at 5 years [22] and 84% at 4 years [24]. The results from our large cohort of patients appear to be more representative and support

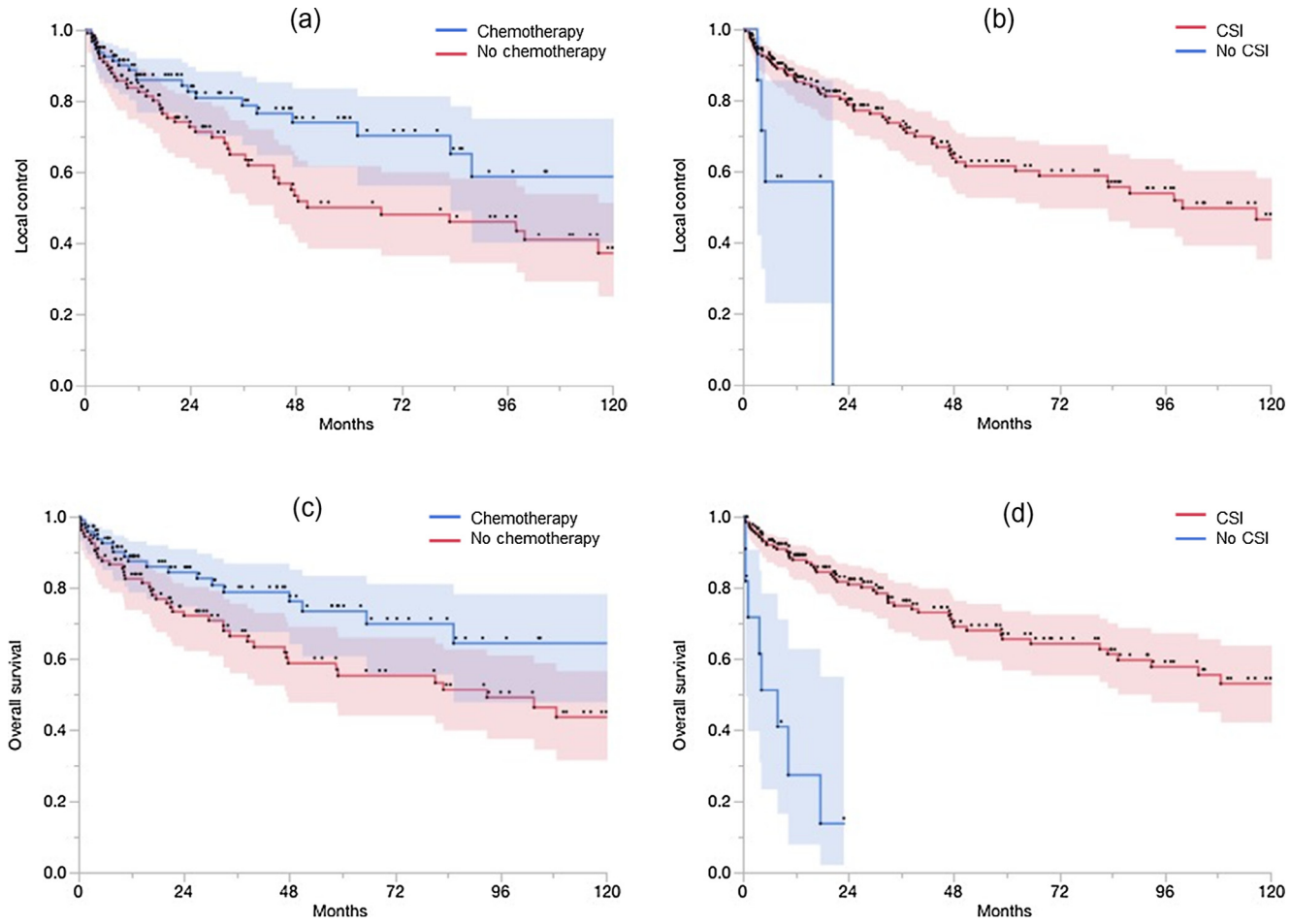

Fig. 2. Impact of CT and CSI. (A and B) Local control. (C and D) Overall survival. CT indicates chemotherapy; CSI, craniospinal irradiation.

Table 4
Statistical Results With Multivariate Analysis.

Significant factors	Local control		Disease-free survival		Overall survival	
	RR	*P* value	RR	*P* value	RR	*P* value
Clinical factor						
KPS score, ≥80 vs <80	2.68	<.001	3.10	<.001	2.58	.01
Therapeutic factors						
Adjuvant CT, yes vs no	1.71	.04	. . .	. . .	. . .	. . .
CSI RT, yes vs no	. . .	. . .	5.23	<.001	5.32	<.001

Abbreviations: CSI, craniospinal irradiation; CT, chemotherapy; KPS, Karnofsky Performance Status; RR, risk ratio; RT, radiotherapy; . . ., not statistically significant.

the use of CT in this population; however, our data did not add further information regarding the use of pre-RT CT, which is no longer used in the treatment of pediatric patients with MB. In a recent study, the National Cancer Data Base (between 2004 and 2012) was used to generate data for 751 adult patients with MB [7]. The results showed that combined postoperative CT and RT are associated with superior overall survival for adult MB than RT alone, after adjustment for multiple demographic and clinical factors. The data also showed a nonsignificant trend for improved overall survival with multi-agent CT compared with single-agent CT but no difference between concurrent or sequential chemoradiotherapy.

On the basis of our results, we recommend the following treatment for adult patients with MB; for RT, we advocate the use of CSI, usually with a cranial boost dose, to the initially involved disease site(s). Most of the cancer centers participating in this study follow this protocol, which has resulted in favorable collective outcomes, which our results across multiple European and American institutions validate. We do not recommend the use of only a local RT field; the results for patients given local RT only were unfortunately similar to the results for those who did not receive any RT (data not shown). Our data showed that the timing of RT after surgery may impact all disease outcome end points, including local control, disease-free survival, and overall survival on univariate analyses; however, none of the results were statistically significant on final, multivariate analyses. These clinical results were likely also dependent on the sequence and timing of adjuvant CT, if given. Regarding surgery, complete resection is certainly preferable, if possible. Our data did suggest that adjuvant therapies, including RT and CT, can salvage and improve outcomes for the small group

of patients who have residual disease or whose surgery may be incomplete (27%) or otherwise inoperable (4%); however, the sample size was small for these 2 groups. On the basis of our results, we recommend a total RT dose of 54 Gy or greater to the posterior fossa (including both CSI and RT boost portions).

Our study had limitations inherent in the design and execution of a retrospective study, including selection bias for treatments based on patient and disease characteristics. First, the population was heterogeneous; however, because of the rarity of adult MB, a multiinstitutional effort was warranted. Second, molecular evaluation was lacking, and a centralized review of all pathologic diagnoses was not possible. Although molecular profiles in pediatric MB (i.e., wingless [WNT], sonic hedgehog [SHH], group 3, and group 4) have been more well defined especially in the recent era, it has been strongly suggested that these risk-stratification groups may carry different prognostic weights in the adult population, especially based on age [25]; in general, adults with medulloblastoma have worse prognoses except in the SHH group, which has a very different distribution than its pediatric tumor counterpart. Third, our study included treatments between 1976 and 2014, and outcomes may be biased because of better, current RT and CT regimens. In addition, some data were not collected consistently, and, most importantly, surgery to RT duration was measured in days; however, substantial effort was spent to collect as complete data as possible. Finally, because multiple institutions were involved retrospectively, toxicity information was not reported. We did not have adverse event or quality-of-life data; they were not collected prospectively; however, no treatment-related death was reported. The timing of CT (before, concurrent, and/or after RT) in our population was heterogeneous, and a wide range of practice patterns was reported. Currently, we do not know how the low- and intermediate-risk groups for adult MB patients should be defined, or if the CSI dose (and the magnitude of reduction) should be reduced while maintaining appropriate clinical effectiveness and tumor control rates. These topics should be the subjects of future clinical investigations.

Conclusion

This study, one of the largest multiinstitutional clinical series for the treatment of adults with MB, has clarified prognostic factors for tumor control and also survival outcomes. Although long-term cure and disease control are possible in about half of patients with MB, this tumor is still aggressive and rare in adults. Further clinical research (including molecular profiling and classification [as in pediatric MB]) and treatment intensification are needed to achieve better outcomes. This study showed that patients with a high KPS score who also received CSI had better disease-free and overall survival. The use of CT was associated with better local control, possibly because of improved radiosensitization; however, radiobiologic correlates and data were lacking from our study. Previously, the addition of CT to CSI was not commonly recommended for adults with MB because of high toxicity profiles. However, our study has shown that the addition of CT for patients with high KPS scores may lead to improved local relapse rates and, thus, to improved survival, which should be confirmed by future work in this area. For both RT and CT, these results serve as the new benchmark for treatment and provide the basis for future prospective clinical trials designed to further improve the outcomes for adult patients with this rare tumor.

An important future trend in oncology will be the quantitative evaluation of multiinstitutional data, either by generating data from a registry or by collaborative evaluation of established institutional protocols. Worldwide, the RCN has been an important and successful model for generating data for these types of collaborative studies and for establishing standards of care and disseminating therapeutic advances for rare kinds of malignant tumors such as MB in adults.

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None.

Conflict of interest

None of the authors has a conflict of interest to disclose for this work.

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