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The Prognostic Factors and Outcome of Adult Medulloblastoma: Where We Stand

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We designed our study to analyze the prognostic factors and treatment outcomes of adult medulloblastoma patients who received postoperative craniospinal irradiation. Fourty-three patients who were treated due to medulloblastoma at Istanbul University, Institute of Oncology between 1990 and 2013 were retrospectively analyzed. All of the patients were older than 18 years, with a median age of 27 years (range, 18–51 years). In 40 (93%) patients, total resection of the tumor was achieved, and 3 (7%) patients had undergone a subtotal tumoral resection. Risk assessment revealed 7 high-risk and 36 standard-risk patients. All patients received postoperative craniospinal irradiation, delivering a median craniospinal dose of 36 Gy, with an additional boost to the posterior fossa up to 54 Gy. Fifteen patients received chemotherapy. The median follow-up was 62 months (range, 3–213 months). The 5-year, 10-year, overall, and disease-free survival rates were 63%, 51%, 66%, and 55%, respectively. Univariate analysis revealed that hydrocephalus, initial local recurrence, subtotal resection in primary surgery, initial Karnofsky performance status $\leq$70, duration of symptoms shorter than 30 days, and primary site dose $<$ 54 Gy were found to be negative prognostic factors. Toxicity was moderate. The main therapy in adult medulloblatoms is craniospinal irradiation following surgery. The prognostic factors and outcomes of the patients in our study are concordant with previous reports in the literature.

Key words: Chemotherapy, adjuvant – Medulloblastoma – Radiotherapy, adjuvant – Treatment outcome

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Medulloblastoma (MB) is an embryonal brain tumor. MB is a common type of pediatric tumor and accounts for 25% of all pediatric brain tumors and 40% of posterior fossa tumors. The median age at diagnosis is 5 years, and 80% of cases are diagnosed in the first 15 years. Nevertheless, MB constitutes only 1% of all brain tumors in adults.[1,2] MB is seen more between the ages of 20 and 34 years in the adult population.[2] In contrast to the pediatric type, MB in adults is encountered with more desmoplastic histology and lateral localization.[3] Due to the high risk of leptomeningeal spread of MB of the pediatric type, craniospinal irradiation (CSI) with or without chemotherapy after maximal tumoral resection became the standard treatment.[4] Pediatric protocols are generally used for the treatment of adult MB. Prognostic factors and treatment results are not very well described because of the rarity of adult MB. We analyzed adult MB patients treated in the last 24 years at our institution in terms of prognostic factors and treatment results.

Materials and Methods

The clinical data of 43 patients who were treated at Istanbul University, Institute of Oncology between 1990 and 2013 were retrospectively analyzed. All of the patients were aged 18 years or older in our series.

Patients characteristics

The median age of our study population was 27 years (range, 18–51 years). The median follow-up was 62 months (range, 3–213 months; Table 1). The symptoms and signs of the patients before surgery are listed in Table 2. Preoperative Karnofsky Performance Status (KPS) was $\leq$70 in 7 patients (16.3%), and KPS was >70 in the remaning 36 patients (83.7%). The degree of the spread of MB was evaluated in 6 patients (14%) with craniospinal computed tomography scanning and in 37 patients (86%) with magnetic resonance imaging. Cytologic evaluation of the cerebrospinal fluid (CSF) was determined to be positive in 1 patient (2.3%) and was determined to be negative in 40 patients (93%). In the remaining 2 patients (4.7%), no cytologic examination of CSF was made. Hydrocephalus was detected in 4 patients (13%) with laterally located tumors and in 5 patients (38%) with centrally located tumors. In 5 patients (11%), total excision was performed through a secondary surgery following the primary surgery due to local recurrences before adjuvant therapy. The median interval between the primary surgery and local recurrence was 3 months (range, 2–7 months) in this group of patients. We describe this group as initial locally recurrent disease.

Surgery, histopathology, and risk groups

Whereas the tumor was located centrally in 13 of 43 patients (30.2%), the tumor was found laterally in the remaining 30 patients (69.8%). In 40 patients (93%), total resection of the tumor was achieved; however, the rest of the group (3 patients; 7%) underwent subtotal tumoral resection. In the latter group, the residual tumor size ranged between 1 and 2 cm. Histopathologic examination revealed 26 (60.5%) desmoplastic tumors, 16 (37.2%) classic type of MB, and 1 (2.3%) large cell/anaplastic tumor. Four (15%) of the desmoplastic tumors were located centrally. T status were found to be T1 in 1 (2.3%) patient, T2 in 41 (95.3%) patients, and T4 in 1 (2.3%) patient. M stages were as follows: M0 in 38 patients (88.4%), M1 in 1 patient (2.3%), M2 in 1 patient (2.3%), M3 in 2 patients (4.7%), and M4 in 1 patient (2.3%). Risk assessment revealed 7 high-risk patients (16.3%), and 36 standard-risk patients (83.7%).

Radiotherapy

All of the 43 patients received postoperative CSI through a ^{60}Co teletherapy machine or 6-MV linear accelerator. Thirty-eight (88.3%) patients received CSI immediately following surgery, and the remaining 5 (11.3%) patients were irradiated with CSI after receiving chemotherapy following the surgical intervention. The median whole cranial dose was 36 Gy (range, 23.4–48 Gy); the median posterior fossa dose was 16 Gy (range, 5.4–30.6 Gy); the median total posterior fossa dose was 54 Gy (range, 41.4–57.6 Gy); the median primary site boost dose was 10 Gy (range, 8–14 Gy); and the median total primary site dose was 54 Gy (range, 42–59.4 Gy). Eleven (25.6%) patients received a median dose of 5.4 Gy (range, 3.6–8 Gy) to the lamina cribrosa and 36 Gy (range, 12.6–32.8 Gy) of the median spinal dose (Table 3).

Chemotherapy

Fifteen (34.9%) of 43 patients received chemotherapy [1 T2M0 patient with subtotal resection; 1 T2M4 patient, 1 T4M3 patient, 1 T2M2 patient, 1 T2M1

Table 1 Patient characteristics

Variable	Patients (%)
Sex	
Female	18 (41.9%)
Male	25 (58.1%)
Age (years)	
18–25	18 (41.9%)
26–35	17 (39.5%)
36–45	6 (14.0%)
>45	2 (4.7%)
Period	
1990–1999	13 (30.2%)
2000–2009	21 (48.8%)
2010–2013	9 (20.9%)
Tumor location	
Central	13 (30.2%)
Lateral	30 (69.8%)
Hydrocephalus	
Present	9 (20.9%)
Absent	34 (79.1%)
Duration of symptoms (days)	
<30	17 (39%)
≥30	26 (61%)
Initial recurrence	
Yes	5 (11.6%)
No	38 (88.4%)
T stage	
T1–2	42 (97.7%)
T3–4	1 (2.3%)
M Stage	
M0	38 (88.4%)
M1–4	5 (11.6%)
Initial KPS	
≤70	7 (16.3%)
>70	36 (83.7%)
Surgical resection	
Total	40 (93%)
Subtotal	3 (7%)
Histology type	
Desmoplastic	26 (60.5%)
Classic	16 (37.2%)
Large cell/anaplastic	1 (2.3%)
Tumor size (cm)	
<4	15 (34.9%)
≥4	28 (65.1%)
Risk group	
Standard risk	36 (83.7%)
High risk	7 (16.3%)
Primary chemotherapy	
Yes	15 (34.9%)
No	28 (65.1%)
Chemotherapy regimen	
Packer	7 (16.3%)
OPEC	7 (16.3%)
Karmustin-vincristine	1 (2.3%)
Postoperative residual tumor	
Yes	3 (7%)
No	40 (93%)
Duration of RT (days)	
<48	19 (44.2%)
≥48	24 (55.8%)
Interval between surgery and start of RT (weeks)	
≤6	21 (49%)
>6	22 (51%)
RT technique	
2D-RT	38 (88.4%)
3D-CRT	3 (7%)
IMRT	2 (4.7%)

3D-CRT, 3-dimensional conformal radiotherapy.

patient, 1 T2M3 patient, and 2 T2M0 patients after secondary surgery due to early recurrence; 2 T2M0 patients with lowered irradiation doses (28.8 Gy/16 fractions, 23.4 Gy/13 fractions); 1 T2M0 patient with anaplastic/large cell histology; and 4 T2M0 patients with standard risk]. Seven patients received the Packer regimen (*i.e.*, vincristine, siklofosfamid, and cisplatin), 6 patients received the OPEC regimen (*i.e.*, cisplatin, etoposid, vinkristin, and cyclophosphamide) prior to irradiation, 1 patient received the OPEC regimen after irradiation, and 1 patient received carmustine plus vincristine after irradiation (Table 4).

Statistical analysis

Disease-free survival (DFS) and overall survival (OS) were measured from the date of surgery to the date of newly occured disease (local recurrence, seeding, or distant metastasis), the last follow-up, or death from any cause. DFS and OS rates were calculated with the Kaplan-Meier method and compared among subpopulations of patients using the log-rank test. Sex, tumor location, hydrocephalus, duration of symptoms, initial local recurrence, initial KPS, operation type, histologic subtype, M

Table 2 Symptoms and neurologic signs

Symptoms and signs	n (%)
Headache	34 (79.1%)
Nausea/vomiting	29 (67.4%)
Diplopia	8 (18.6%)
Unsteady gait	21 (48.8%)
Dizziness	17 (39.5%)
Speech disturbance	3 (7%)
Ataxia	23 (53.5%)
Nystagmus	36 (83.7%)
Rhomberg	7 (16.3%)
Dysmetria	11 (25.6%)
Sixth cranial nerve palsy	3 (7%)
Dysdiadocokinesia	6 (14%)

Table 3 RT treatment fields and doses

Treatment field and dose	Median (range)
Cranial irradiation dose (Gy)	36 (23.4–48)
Fractions	20 (13–17)
Posterior fossa boost irradiation dose (Gy)	16 (5.4–30.6)
Fractions	8 (3–17)
Total posterior fossa irradiation dose (Gy)	54 (41.4–57.6)
Fractions	30 (21–33)
Primary site boost irradiation dose (Gy)	10 (8–14)
Fractions	5 (4–7)
Total primary site boost irradiation dose (Gy)	54 (42–59.5)
Fractions	30 (22–33)
Lamina cribrosa irradiation dose (Gy)	5.4 (3.6–8)
Fractions	3 (2–4)
Spinal irradiation dose (Gy)	36 (12.6–37.8)
Fractions	20 (7–24)

stage, tumor size, risk group, chemotherapy, radiotherapy (RT) duration, interval between surgery and RT, cranial RT dose, posterior fossa RT dose, primary site RT dose, and spinal RT dose were all taken as prognostic factors in univariate analysis.

Results

Survival and patterns of recurrence

OS for 2-year, 5-year, 8-year, and 10-year survival was 86%, 63%, 51%, and 51%, respectively (Fig. 1a). DFS for 2-year, 5-year, 8-year, and 10-year survival was 83%, 66%, 59%, and 55%, respectively (Fig. 1b). There were 16 patients (6 women and 10 men) with recurrences during a median follow-up of 62 months (range, 3–231 months). In 13 of 16 patients with recurrences, the tumor diameter was greater than 4 cm. Fifteen patients died from recurrent disease, and only 1 patient is alive with recurrent disease. The median DFS among this group of 16 patients was 29 months (range, 5–99 months), and the median OS was 41 months (range, 14–99 months). Ten of 16 patients developed isolated local recurrence, 1 patient had local recurrence and spinal seeding metastasis, and 1 patient developed local recurrence and bone metastasis. The median interval between surgical intervention and local recurrence was 40 months (range, 14–99 months). One patient received only supportive treatment among the recurrent group, 4 patients underwent surgical resection, 5 patients received chemotherapy after surgery, 1 patient received chemotherapy and RT after surgery, and 1 patient underwent stereotactic radiosurgery due to recurrent disease. Four of 16 patients with local recurrences developed distant metastasis, and all of them received chemotherapy (Table 5).

Table 4 Chemotherapy regimens

Chemotherapy type	Patients (n)
Packer regimen	7
OPEC regimen	7
BCNU-vincristine	1
Total	15

BCNU, carmustine.

Prognostic factors

Univariate analysis revealed that hydrocephalus, initial locally recurrence, subtotal resection in primary surgery, initial KPS of $\leq$70, duration of symptoms shorter than 30 days, and primary site dose $<$54 Gy were negative prognostic factors (Table 6).

Toxicity

Alopesia, nausea, and hematologic disturbances were observed due to irradiation. In 6 patients, mild memory problems were detected. Three patients developed pancytopenia, and 1 of them died of sepsis. We also detected grade 2 neuropathy in 1 patient, grade 3 neuropathy in another patient, thrombocytopenia of grade 2 in 4 patients, and thrombocytopenia of grade 3 in 1 patient. In a total of 10 patients with hematologic toxicity, 8 of them received chemotherapy (4 OPEC regimen and 4 Packer regimen).

Discussion

We retrospectively analyzed the prognostic factors and outcome of adult patients with MB located in the posterior fossa of the cranium treated at a single center. MB is obviously seen more rarely in adults than in the pediatric population. Basically, more lateral localization and desmoplastic hystology are encountered. In fact, a previous series of adult MB reported about 29%–71% of lateral localization incidence and 25%–50% of desmoplastic hystology.[2,5–10] In our study, we found similar localizations and hystologic types to previous reports in the literature (69.8% lateral localization and 60.5% desmoplastic hystology).

Late recurrences of MB are more frequent in adults compared with pediatric patients. Whereas pediatric relapses are usually seen in the first 2 years, the median time of MB recurrences in adults

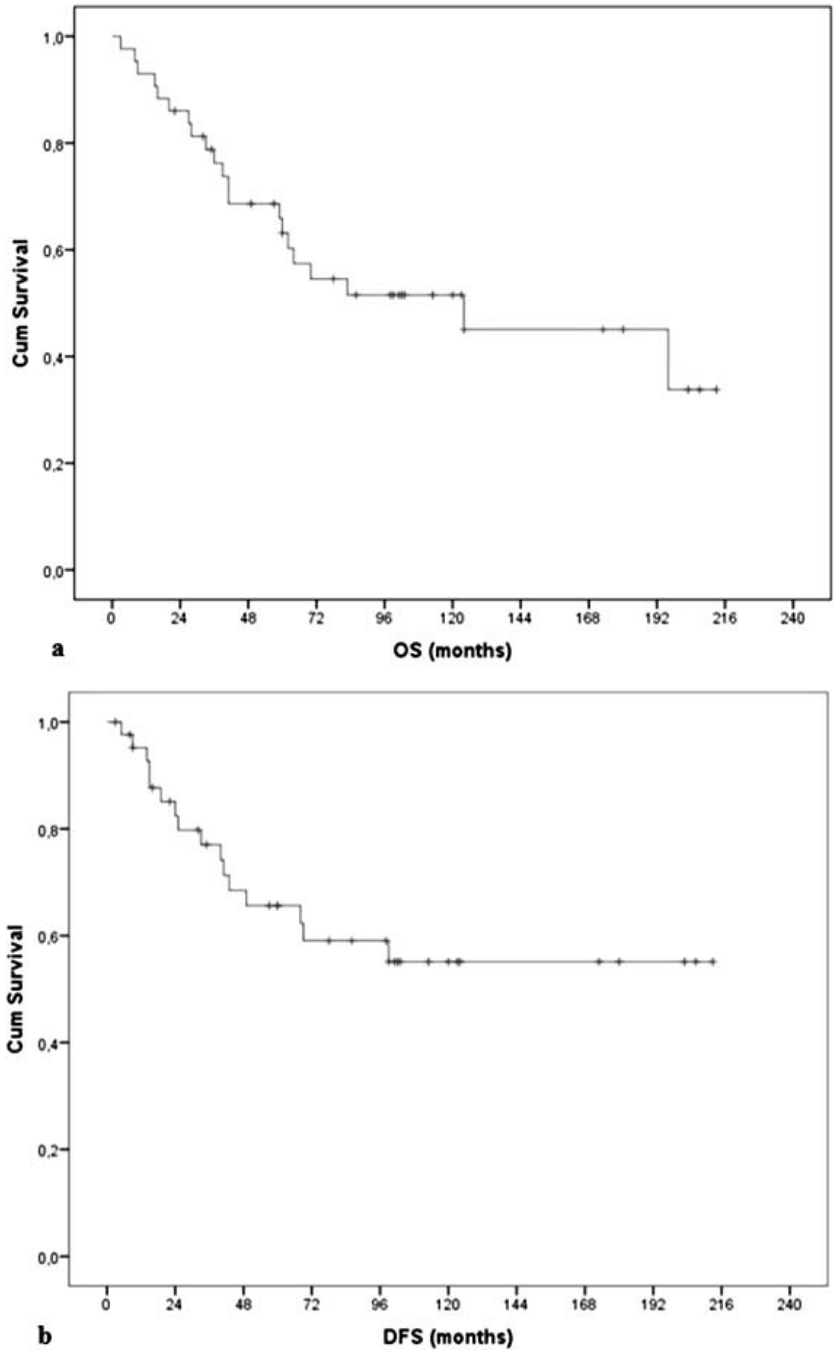

Fig. 1 Kaplan-Meier curves: (a) OS and (b) DFS.

is 26 months. Twenty-nine percent of the remaining patients with MB recurrences are detected later than 5 years.[2] The posterior cranial fossa remains the most frequent site of relapse in both age groups.[2,11–13] There were 16 patients with recurrences (10 of them with only local recurrence) in our series, with a median DFS of 29 months and a median OS of 41 months. Jereb *et al* showed 40 recurrences in 53 patients with MB (13 patients were older than 16 years). The most frequent site of relaps was the posterior fossa (53%), and the second most frequent site was cribriform plate area (15%).[14] After this study, they also modified their treatment field and suggested a new irradiation treatment field including the cribriform plate area after completing a new study with 15 patients with MB who were irradiated according to the new target area covering the cribriform plate.[15]

Table 5 Recurrence pattern

Site of recurrence	Patients (n)
Only posterior fossa	10
+ Spinal seeding	1
+ Bone	1
Cerebellar + spinal seeding	1
Cerebral seeding + bone	1
Bone	1
Bone + bone marrow	1
Total	16

Donahue *et al* evaluated the quality of RT in the Children's Cancer Group/Pediatric Oncology Group 9961 and analyzed associations of RT deviations with outcome. The cribriform plate region was the most common deviation in 79 (25.6%) of 308 patients, and the posterior fossa was the second most common site of deviation (27 of 308 patients; 8.8%). These deviations in the posterior fossa resulted from treating less than the whole posterior fossa. No significant differences in DFS and OS were detected between patients with RT deviations and those without.[16] In our study, 11 patients received boost irradiation to the lamina cribrosa (median dose, 5.4 Gy; range, 3.6–8 Gy). None of the 43 patients developed recurrences in the lamina cribrosa region, and no differences according to OS and DFS were seen among patients in our series.

Chang *et al* showed in their retrospective single center study that the complete resection of adult MB has a positive effect on OS and DFS.[2] Whereas we were able to show that the complete surgical resection has a positive effect on DFS for 5 years (68% versus 33%; $P = 0.02$), no statistically significant effect was found for OS.

The treatment strategy of MB in children, which includes CSI, boost irradiation to the posterior fossa, and chemotherapy following maximal possible tumor resection, is very well described. DFS in children with MB is reported as 75% to 85% in previous studies.[17,18] Retrospective series of adult MB has had significant lower 5-year OS rates (40%–84%) and lower DFS rates (32%–63%) in comparison to pediatric patients with MB.[2,6,8,9,12,19–22] This was similar to the population-based study of Lai *et al*, which included 454 adult MB patients with 2-, 5-, and 10-year OS rates of 79.9%, 64.9%, and 52.1%, respectively.[23] We found OS rates of 86%, 63%, and 51% for 2, 5, and 10 years, respectively.

Successful results were achieved after lowering the traditional neuroaxis RT dose of 36 to 23.4 Gy by adding chemotherapy in pediatric patients with standard risk.[17,24] In the course of conventional RT of anatomic posterior fossa, 35% of the entire brain and 60% of each of 2 temporal lobes received irradiation.[25] Merchant *et al* were successful in decreasing the toxicity as a consequence of whole posterior fossa irradiation by lowering the CSI dose to 23.4 Gy, conformal posterior fossa dose to 36 Gy, and conformal primary site dose to 55.8 Gy, followed by 4 cycles of high-dose chemotherapy in 86 patients with standard risk between 3 and 21 years.[26] With these modification of the previous technique, the estimated 5-year event-free survival and the cumulative incidance of posterior fossa failure rates were changed to 83 ± 5.3% and 4.9 ± 2.4% (±SE), respectively. They were able to show in their study that the median volume of posterior fossa receiving a RT dose more than 55 Gy was decreased by 13%, and they also showed a significant decrease in RT dose received by the temporal lobe, cochleae, and hypothalamus during irradiation. Posterior fossa RT dose was determined to be a significant prognostic factor.[7,8,20] In our series, 12 patients received primary site boost irradiation following posterior fossa irradiation and CSI. However, neither spinal nor cranial RT dose reduction was made. In this subgroup of 12 patients, median spinal, median cranial, median posterior fossa boost, and median primary site boost doses and dose ranges were 36 (range, 36–37.8), 36 (range, 36–38), 9.75 (range, 5.4–14), and 10 Gy (range, 8–14 Gy), respectively. The median primary site dose was 54 Gy (range, 42–59.4 Gy) in our study. The retrospective evaluation of our series revealed that median primary site doses lower than 54 Gy seem to be associated with a negative effect on 5-year OS (25% versus 67%; $P = 0.04$).

Wong *et al* reported 21 months as the median OS in *de novo* patients with high risk and 15 months as the median OS in patients with recurrent disease (3 recurrent cases; maximal tumor resection; but 1 patient with a residual tumor greater than 1.5 cm in size).[27] We have seen that there was no residual tumor after secondary maximal tumor resection for initial recurrence. Despite that, it has a negative effect on OS ($P = 0.01$).

Kocakaya *et al* recently published a meta-analysis including 227 publications covering 907 adult MB patients between 1969 and 2013, and they found that the median survival was 65 months and 5-year OS was 50.9%. The meta-analysis revelaed that the patients receiving first-line chemotherapy lived significantly longer [median OS, 108 months; 95% confidence interval (CI), 68.6–148.4] than patients treated with RT alone (median OS, 57 months; 95%

Table 6 Univariate analysis of risk factors for OS and DFS

		OS			DFS		
Variable	Patients (n)	5-year OS (%)	10-year OS (%)	*P* value	5-year DFS (%)	10-year DFS (%)	*P* value
Sex							
Female	18	61	54	0.82	63	63	0.69
Male	25	65	50		67	50	
Tumor location							
Central	13	59	49	0.77	77	62	0.36
Lateral	30	66	53		61	53	
Hydrocephalus							
Present	9	44	22	0.01	30	15	<0.01
Absent	34	68	60		74	66	
Duration of symptomps (days)							
<30	17	45	32	0.03	48	40	0.07
≥30	26	75	65		75	63	
Initial local recurrence							
Yes	5	20	20	0.01	37	NE	0.16
No	38	69	58		68	60	
Initial KPS							
≤70	7	28	14	0.01	18	NE	<0.01
>70	36	70	60		75	62	
Operation							
Complete	40	63	56	0.14	68	60	0.02
Subtotal	3	33	NE		33	NE	
Histology type							
Classic	16	66	59	0.54	70	53	0.62
Desmoplastic	26	55	45		61	55	
M stage							
M0	38	64	51	0.88	67	55	0.69
M1–4	5	50	50		60	60	
Tumor size							
<4 cm	15	70	53	0.19	77	77	0.11
≥4 cm	28	60	42		60	44	
Risk							
Standard	36	65	54	0.51	71	59	0.09
High	7	50	33		38	38	
Chemotherapy							
Yes	15	51	38	0.20	66	52	0.73
No	28	70	57		65	56	
Duration of RT (days)							
≤48	19	71	57	0.32	77	57	0.54
>48	24	58	48		57	52	
Interval between surgery and start of RT (weeks)							
≤6	21	54	54	0.52	50	45	0.38
>6	22	78	55		76	57	
Kranyal RT dose							
≤36 Gy	31	62	53	0.92	65	60	0.71
>36 Gy	12	67	50		67	46	
PF dose							
<54 Gy	15	55	44	0.57	81	68	0.27
≥54 Gy	28	67	54		59	50	
Primary site dose							
<54 Gy	5	25	NE	0.04	81	68	0.27
≥54 Gy	38	67	55		59	50	
Spinal dose							
<36 Gy	8	50	50	0.44	51	51	0.48
≥36 Gy	35	66	53		68	56	

NE, not evaluated; PF, posterior fossa.

CI, 39.6–74.4) or patients who received chemotherapy at the time of tumor recurrence.[28] We could not show any significance in OS between patients who received chemotherapy (35% of patients; median OS, 83 months; 95% CI, 3.18–162.8) or did not (median OS, 124 months; 95% CI, 9.7–238.3).

Effectivity and toxicity of different treatment strategies in pediatric and adult MB patients with new treatment modalities, such as intensity modulated RT (IMRT), proton therapy, or carbon ion irradiation, which give us the chance to decrease the radiation doses delivered to the organs at risk, have been studied.[29–32] Yock *et al* recently reported their phase II prospective clinical study related to the long-term toxic effects of proton RT including 59 pediatric MB patients, acceptable toxicity rates, and similar survival outcomes.[33] Brown *et al* treated 19 adult MB patients with proton CSI and the remaining 21 patients with photon CSI.[33] The patients treated with proton CSI experienced less weight loss that was greater than 5%, less grade II nausea and vomiting, less esophagitis, and less reduction in peripheral white blood cells, hemoglobin level, and platelets compared with the patients treated with photon CSI. Therefore, this was the first report revealing that proton beam CSI significantly reduces gastrointestinal and hematologic toxicities.

The prognostic factors and outcomes of the patients in our study are concordant with previous reports in the literature. However, we need multi-institutional studies with randomized patients to assess the optimal RT strategy and the timing of chemotherapy for adult MB with minimal toxicity.

In conclusion, the main therapy in adult MB is CSI following surgery. The presence of hydrocephalus, initial local recurrence, initial KPS $\leq$70, subtotal surgical resection, shortness of duration of symptoms, and primary site dose $<$54 Gy are negative prognostic factors. There was no randomized trial about chemotherapy use in adult MB. Nevertheless, an actual meta-analysis showed survival benefits with chemotherapy use for adult MB. Previous data about the RT strategies for adult MB collected from studies which used 2-dimensional (2D) or 3D conformal RT. Nowadays, IMRT, proton, and carbon ion RT or molecular variants for the treatment of MB in adults are promising technologies.

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