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Expertise is crucial to prolong survival in average risk medulloblastoma: long-term results of a retrospective study

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Abstract

Purpose: Medulloblastoma is a rare tumor in adults and the use of adjuvant chemotherapy in average risk patients is debated.

Methods: Patients included in our study were ⩾16 years of age, had histologically confirmed medulloblastoma, and underwent adjuvant radiotherapy with or without chemotherapy. Average risk was defined according to the Chang classification.

Results: We included 48 average-risk patients. Median follow-up was 151.5 months (95% confidence interval, 124.5–178.5). Both progression-free survival (PFS) and overall survival (OS) were significantly influenced by adjuvant chemotherapy (PFS: hazard ratio [HR], 0.334, $p = 0.05$; OS: HR, 0.187, $p = 0.017$) and by receiving the treatment in a referral center (PFS: HR, 0.250, $p = 0.008$; OS: HR, 0.295, $p = 0.038$).

Conclusions: Treating patients with average-risk medulloblastoma in a referral center improves both PFS and OS, does adding adjuvant chemotherapy.

Keywords

Medulloblastoma, average-risk medulloblastoma, reference center, expertise, rare tumor, adjuvant therapy

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Introduction

Medulloblastoma is the most common malignant embryonal neoplasm of the central nervous system (CNS) in children. It accounts for 15%–25% of all childhood brain tumors with an incidence peak around 9 years of age at diagnosis. It is rare in adults (less than 1% of primitive CNS tumors), for whom its incidence is 0.6–1 case per million per year.[1–12]

Correct staging with brain magnetic resonance imaging (MRI) performed before and after surgery (within 48 hours), spine MRI (whenever possible presurgery, alternatively after surgery), and cerebrospinal fluid (CSF) cytology performed 15–20 days after surgery is essential for staging and treatment.

Tumors are classified for their extension and site of origin (T) and absence or presence of metastasis inside or outside the neuraxis (M) according to the Chang staging system.[4] Once correctly staged, patients are usually divided into average and high-risk groups.

The average-risk group presents no metastases (M0) and no residual disease after surgery (defined as >1.5 cm^2). High-risk patients have metastases or residual disease.[3]

Standard treatment for adult patients is represented by surgical resection and craniospinal irradiation (36 Gy in 20 fractions) and posterior fossa boost of 18.8 Gy in 11

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fractions. In case of M3 spinal disease, the dosage to the spine is 39.6 Gy in 22 fractions.[5] In high-risk patients, radiotherapy treatment is followed by adjuvant chemotherapy. The role of chemotherapy for average-risk adult patients remains controversial.

Large retrospective series have provided information about clinical outcomes of adult patients with medulloblastoma. However, data about prognostic risk factors of average-risk patients remain few and controversial. Some authors concluded that outcomes and risk factors are similar in children and adults, while others showed that prognostic factors in adult medulloblastoma are not comparable to those in children.[5]

We performed a study to evaluate progression-free survival (PFS), overall survival (OS), and prognostic factors of adult patients with average-risk medulloblastoma presenting at our institution.

Materials and methods

All patients included in our study were ⩾16 years of age, had histologically confirmed medulloblastoma, and underwent adjuvant radiotherapy with or without chemotherapy. Average risk was defined as postsurgical residual ⩽1.5 cm^2 and no metastatic disease (M0) according to Chang classification.

The patients were staged with brain MRI and, whenever possible, preoperative spine MRI; otherwise, spine MRI was performed after surgery. In all patients, postsurgical MRI scan with contrast enhancement was routinely used to define residual disease within 48–72 hours from surgery. CSF cytology was obtained at least 15 days from surgery. Radiotherapy was administered with doses of 36 Gy in 20 fractions on the cranio-spinal axis plus a boost of 18 Gy in 10 fractions on the posterior cranial fossa (total dose 54 Gy).

Chemotherapy regimens were cisplatin (25 mg/m^2 on days 1–4) plus etoposide (40 mg/m^2 on days 1–4) and cisplatin (25 mg/m^2 on days 1–4) plus etoposide (40 mg/m^2 on days 1–4) with cyclophosphamide (1000 mg/m^2 on day 4) before January 2010 or without this agent (after January 2010). The administration of cyclophosphamide was avoided to reduce systemic toxicity and due to an uncertain clinical efficacy in this setting.

Cranial and spinal MRI was repeated every 2 cycles in the course of treatment. After adjuvant chemotherapy, a brain MRI was performed every 3 months for the first year while spine MRI was performed every 6 months. The brain and spine MRI were than performed every 6 months for up to 5 years and yearly thereafter. After the identification of disease recurrence, patients underwent MRI studies of the entire neuroaxis and CSF cytology. This was a retrospective study approved by the Ethical Committee of the Emilia Romagna region (approval number CE 17047) and performed in accordance with national law, institutional ethical standards, and the 1964 Helsinki Declaration and its later amendments.

Statistical analysis

Data are reported as means, ranges, and frequencies. The Fisher exact and Kruskal-Wallis tests were applied. Survival data (median survival times with 95% confidence interval [CI]) were computed through Kaplan-Meier procedure and analyzed by means of the log-rank test. Hazard ratios (HRs) were computed together with their 95% CIs. PFS and OS were computed from the time of surgery to the first progression or death, respectively, or to the date of the last follow-up or contact. SPSS (version 13.0 for Windows; SPSS Inc.) was used as statistical package. Two-tailed p values less than 0.05 were considered significant.

Results

We included 48 average-risk patients diagnosed from 1988 to 2016. Median age was 29 years (range 16–61); M/F ratio was 26 (54.2%)/22 (45.8%). The most represented histologies were classic in 15 patients (31.3%) and desmoplastic in 15 patients (31.3%). Five patients had extensive nodularity (10.4%) and 2 patients had large cells/anaplastic histology (4.2%).

Twenty-four patients (50%) received only adjuvant radiotherapy and 24 (50%) also received chemotherapy. Thirty were treated in our institution (62.5%) and 18 were followed-up in our institution after having received treatment in other centers.

Patient characteristics are summarized in Table 1.

After a median follow-up of 151.5 months (95% CI, 124.5–178.5), 14 patients had disease progression and 13 patients died, 12 of disease and 1 of other cause (disease unrelated, considered censored at the time of the event). Relapses, detected by MRI, were mainly in the CNS: spine (6/14), cerebellum (6/14), bone (3/14). None of these patients received adjuvant chemotherapy.

Progression-free survival

Median PFS was 9 years in patients who received radiotherapy alone and was not reached in those who received radiotherapy and chemotherapy. This benefit was more significant after 10 years from diagnosis: PFS at 10 and 15 years (PFS-10 and -15) were both 38.5% ± 13.0% in the radiotherapy alone group vs 82.3% ± 8.0% in the radiotherapy and chemotherapy group (HR, 0.334; 95% CI, 0.105–1.068, $p = 0.05$) (Table 2, Figure 1).

Median PFS was not reached in patients who were treated in our institution (referral center) and was 9 years for those who had received treatment in other centers. PFS-15 in referral center vs other centers was 72.1% ± 10.1% vs 34.3% ± 17.2% (HR, 0.250; 95% CI, 0.084–0.745; $p = 0.008$) (Figure 2).

Sex ($p = 0.800$), age (⩽ or > 25 years) ($p = 0.157$), delay of radiotherapy (> 6 weeks from surgery) ($p = 0.600$),

Table 1. Patient characteristics.

	Chemotherapy	No chemotherapy	Total
N	24	24	48
Age, y	29 (16–61)	34 (16–57)	30 (16–61)
M/F	13/11	13/11	26/22
Histology			
Classic	7 (29.2)	8 (33.3)	15 (31.3)
Desmoplastic	6 (25.0)	9 (37.5)	15 (31.3)
Extensive nodularity	3 (12.5)	2 (8.3)	5 (10.4)
Large cell	1 (4.2)	1 (4.2)	2 (4.2)
Unknown	7 (29.2)	4 (16.7)	11 (22.9)
Treatment center			
Referral			30 (62.5)
Other			18 (37.5)
Timing of RT (from surgery), wk			
<6			13 (27.1)
>6			35 (72.9)
Chemotherapy regimen			
DEC	16 (66.7)		
CDDP-VP16	5 (20.8)		
Temozolomide	1 (2.1)		
MOPP	1 (2.1)		
Unknown	1 (2.1)		
Timing of chemotherapy			
Pre-RT	10 (41.7)		
Pre and post-RT	6 (25)		
Post-RT	8 (33.3)		
Relapse site			
Spine			5 (35.7)
Cerebellum			6 (42.9)
Bone			2 (14.3)
Spine and bone			1 (7.1)

RT: radiotherapy.
Values are mean (range) or n (%).

Table 2. Progression-free survival (PFS) and overall survival (OS) rates at 5, 10, 15, and 20 years.

	RT + CT, %	RT, %
PFS-5	86.9 ± 7.1	87.3 ± 6.9
PFS-10	82.3 ± 8.0	46.2 ± 13.1
PFS-15	82.3 ± 8.0	38.5 ± 13.0
PFS-20	82.3 ± 8.0	38.5 ± 13.0
OS-5	95.2 ± 4.6	95.7 ± 4.3
OS-10	89.3 ± 7.2	74.1 ± 10.3
OS-15	89.3 ± 7.2	52.0 ± 13.1
OS-20	89.3 ± 7.2	41.6 ± 14.0

CT: chemotherapy; RT: radiotherapy.

chemotherapy with or without cyclophosphamide ($p = 0.562$), and timing of chemotherapy (preradiotherapy or postradiotherapy) ($p = 0.360$) did not correlate with PFS.

Chemotherapy-related all-grade toxicity occurred in 15 (62.5%) of 24 patients. Almost all adverse events reported consisted of hematologic toxicity with the exception of two patients who developed grade 1 ototoxicity. Overall, 8 (33.3%) patients presented grade 3–4 toxicity with 2 cases of grade 4 neutropenia. No toxicity-related death occurred. There was no difference in terms of all-grade toxicity between patients treated in our institution and those treated in other centers (57.0% vs 75.0%; $p = 0.373$). Similarly, there was no difference in terms of grade 3 or higher toxicity between our institution and other centers (37.5% vs 31.2%; $p = 0.142$).

Overall survival

Median OS was 18 years (95% CI, 89.0–344.1) in patients who received radiotherapy alone and was not reached for patients treated with radiotherapy and chemotherapy. OS-10 was74.1% ± 10.3% in the radiotherapy group vs 89.3% ± 7.2% in the radiotherapy and chemotherapy group. OS-15 was 52.0% ± 13.1% in the radiotherapy alone group vs 89.3% ± 7.2% in the radiotherapy and

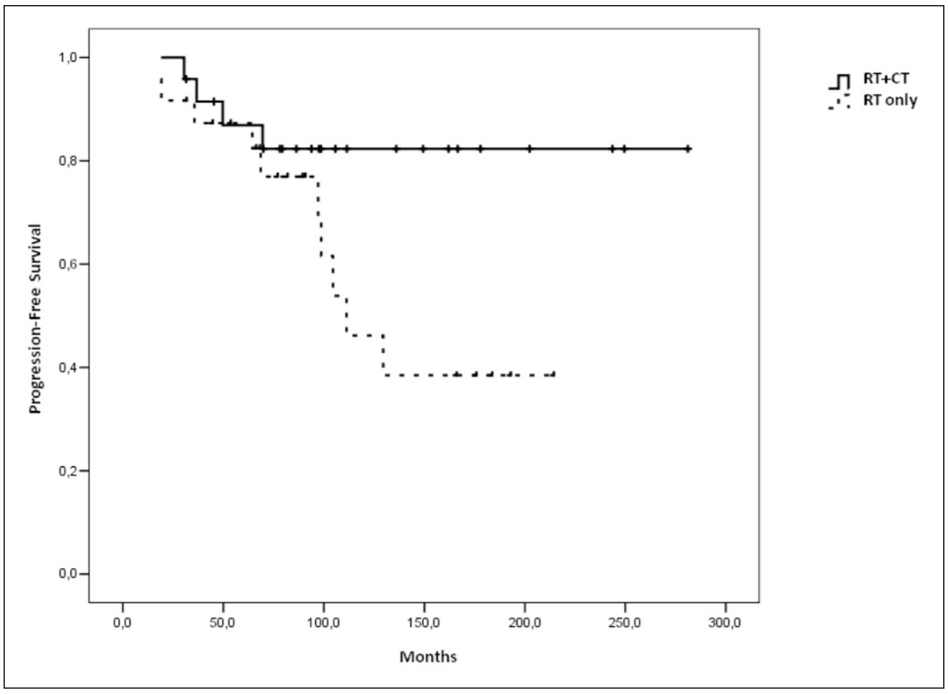

Figure 1. Progression-free survival according to treatment. CT: chemotherapy; RT: radiotherapy.

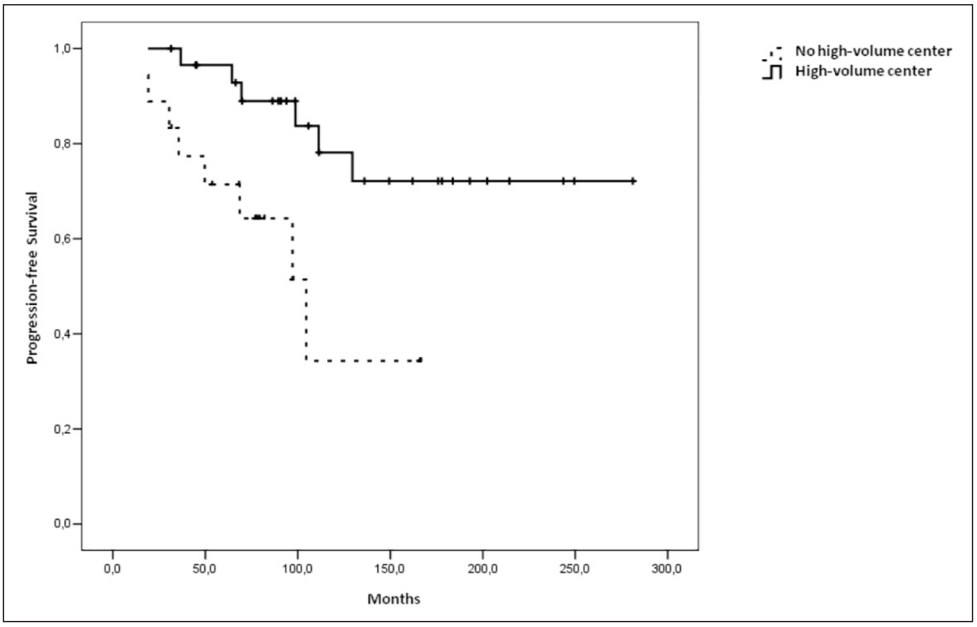

Figure 2. Progression-free survival according to treatment center.

chemotherapy group (HR, 0.187; 95% CI, 0.040–0.872; $p = 0.017$) (Table 2, Figure 3).

Median OS was not reached in patients treated in the referral center vs 18 years in patients treated outside the referral center. OS-15 and OS-20 were 78.8% ± 8.5% and 78.8% ± 8.5 in patients treated in the referral center and were 56.8% ± 16.4% and 0% in patients treated outside the referral center (HR, 0.295; 95% CI, 0.087–0.997; $p = 0.038$) (Figure 4).

Sex ($p = 0.289$), age (⩽ or >25 years) ($p = 0.472$), delay of radiotherapy (> 6 weeks from surgery) ($p = 0.721$), chemotherapy regimen (with or without cyclophosphamide) ($p = 0.655$), and timing of chemotherapy (before or after radiotherapy) ($p = 0.428$) did not correlate with OS.

Because referral center and adjuvant chemotherapy were the only factors influencing survival, we evaluated

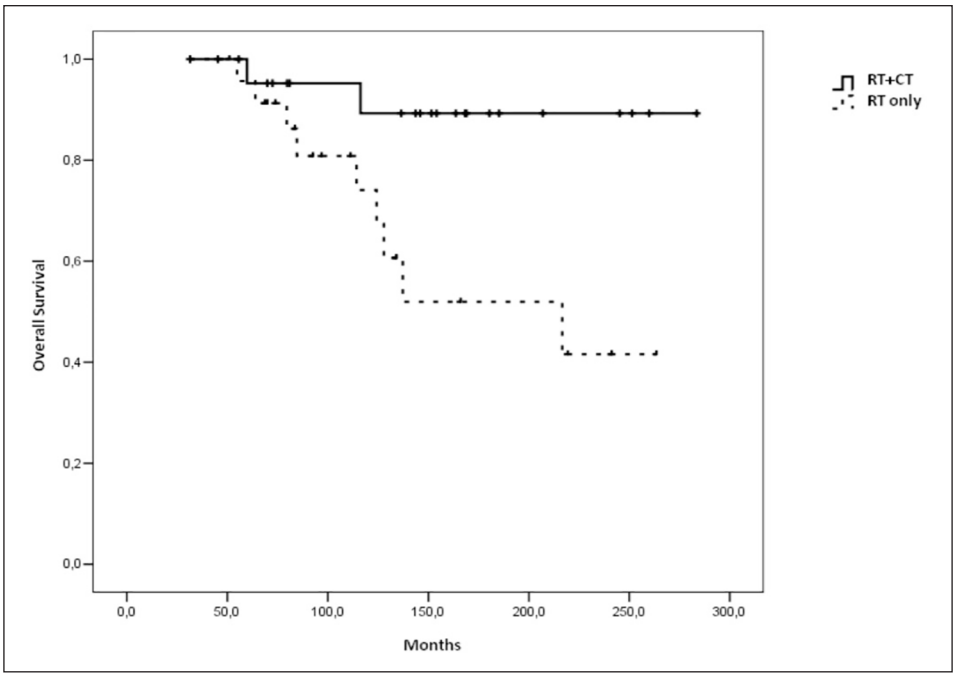

Figure 3. Overall survival according to treatment. CT: chemotherapy; RT: radiotherapy.

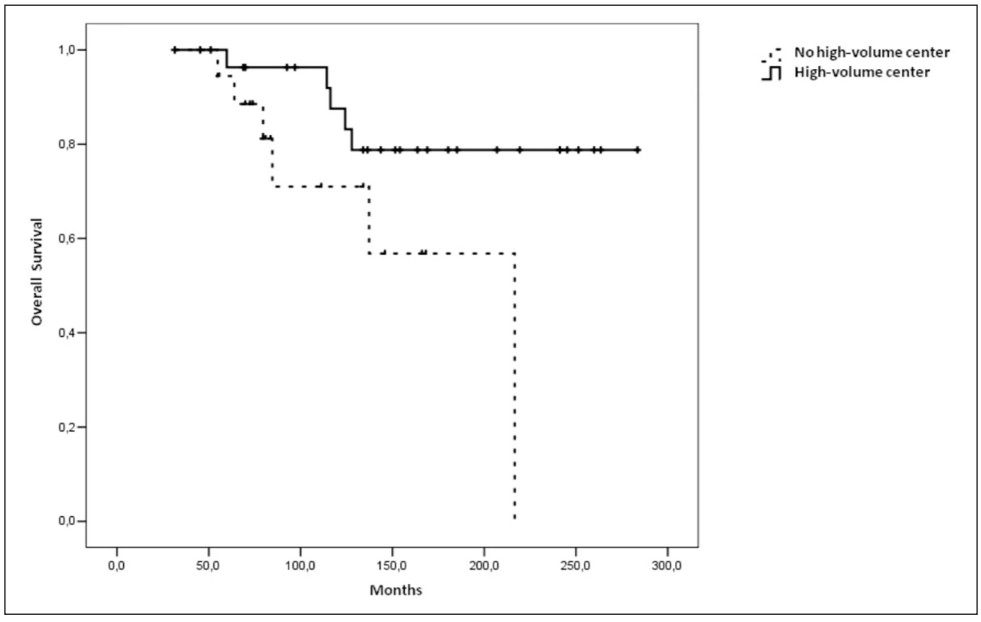

Figure 4. Overall survival according to treatment center.

the correlation between these variables, and did not find a significant correlation ($p = 0.135$).

Discussion

The standard treatment for patients with average-risk medulloblastoma includes, whenever possible, radical surgery and radiation therapy. In children, craniospinal irradiation is frequently complicated by long-term sequelae and toxicities due to the good prognosis and long life expectancy. In the management of young average-risk patients with medulloblastoma, chemotherapy has been added in the attempt to reduce total dose of radiotherapy delivered to brain and spinal cord and to limit toxic effects. Packer et al.[13,14] reported positive results in their trial in which children with nondisseminated medulloblastoma were treated with postoperative reduced-dose craniospinal irradiation (23.4 Gy in 13 fractions) with a boost to the

posterior fossa (31.8 Gy in 17 fractions) with concomitant vincristine and adjuvant chemotherapy with lomustine, vincristine, and cisplatin. This schedule resulted in better tolerance and good safety and currently represents the multimodal treatment of average-risk patients older than 3 years and younger than 18 years.[13,14]

Due to the rarity of the disease in adults, data are mostly provided by retrospective studies. Randomized trials are not available. In the prospective study by Brandes et al.,[3] average-risk patients were treated with radiotherapy alone and high-risk patients were treated with radiotherapy and chemotherapy. PFS at 5 years in low-risk patients was 76% ± 14% (95% CI, 52%–100%). Padovani et al.[15] found no survival difference between average-risk patients treated with radiotherapy alone (axial doses ⩾34 Gy) and average-risk patients treated with radiotherapy in combination with chemotherapy (axial doses <34 Gy). In a large retrospective study of 751 adult patients (median age 29 years; range 18–85) with medulloblastoma (88% with M0 disease), patients received postoperative craniospinal irradiation and chemotherapy with a significant benefit (OS 5 years, 86% vs 72%, $p < 0.0001$).[16]

In an international retrospective study of 206 patients with adult medulloblastoma (62% with M0 disease), 48% of patients also received chemotherapy. Patients receiving systemic chemotherapy showed improved local control and survival.[17]

We found a statistically significant benefit from adding adjuvant chemotherapy to radiotherapy in terms of OS and PFS in average-risk patients.[18] Patients treated with both radiotherapy and adjuvant chemotherapy had a 15-year OS and PFS of 89.3% and 82.3%, respectively; patients receiving radiotherapy alone had 52.0% ($p = 0.02$) and 38.5% ($p = 0.05$) 15-year OS and PFS.

Despite the limitations of our analysis due to the small sample size, the addition of cyclophosphamide to cisplatin-VP16 protocol did not seem to have prognostic significance in terms of PFS ($p = 0.562$) and OS ($p = 0.655$). Currently it is not included in the chemotherapeutic protocols for medulloblastoma treatment. All patients treated in other centers received regimens containing cyclophosphamide. As mentioned in the Methods, in our institution we have avoided cyclophosphamide since 2010, preferring administration of cisplatin and VP16 alone. Although other centers adopted regimens containing cyclophosphamide, the median number of cycles was similar to those administered in our institution (median of 4 cycles after radiation therapy). Similarly, there was no significant difference in the time of chemotherapy start.

Another controversial argument is the impact of time interval between surgery and radiotherapy on survival. It has been reported that delaying radiotherapy for more than 5 weeks seems to be associated with worse local control and prognosis.[8] Abacioglu et al.[9] concluded that the best time for radiotherapy should be between 3 and 6 weeks from surgery. Other reports did not confirm a detrimental effect of delaying radiotherapy in children and adult patients.[9] Our data did not show a correlation between delaying radiotherapy for more than 6 weeks and patients' outcomes ($p = 0.600$ for PFS and 0.721 for OS).

Comparing the outcomes of patients treated in our institution, a referral center, and those treated in other centers, we showed higher survival rates (OS-15, 78.8% vs 56.8%, $p = 0.038$; PFS-15, 72.1% vs 34.3%, $p = 0.008$), suggesting that treatment in referral centers should improve survival, as in other rare tumors.[19–21] Due to the rarity and complexity of management of adult medulloblastoma, these patients should be treated at centers with a great deal of experience.

Notably, according to the 2016 World Health Organization classification, diagnosis of medulloblastoma must be defined by an integrated histologic and molecular assessment. As already reported, histologic diagnosis involves four medulloblastoma entities: classic, desmoplastic or nodular, extensive nodular, or large cell/anaplastic medulloblastoma. At the molecular level, medulloblastoma comprises four entities: WNT-activated (classic), SHH-activated TP53 wild-type (generally desmoplastic or nodular medulloblastoma or extensive nodular tumor), SHH-activated TP53 mutated (large anaplastic and less often desmoplastic or nodular medulloblastoma), and the non-WNT and non-SHH (classic or anaplastic) medulloblastoma.[4] In adults, the most frequent variant reported is the SHH-activated TP53 wild-type medulloblastoma; WNT-activated medulloblastoma can be found in only 15% of cases.[4]

Possible biases of our study could derive from limited sample size and from the unavailability of pathologic subtypes for the whole population. The strength of our study lies in the long follow-up period, which is essential to evaluate prognosis in this group of patients with long life expectancy and late relapses.

Conclusions

In our study, we found a significant survival benefit by adding adjuvant chemotherapy to surgery and radiotherapy. An important issue that deserves further investigation is the possibility to reduce the dose of radiotherapy in adult patients receiving chemotherapy, decreasing treatment-related neurologic, endocrinologic, and gastrointestinal morbidities. This should be an important end point of treatment of these long-term survivors and will be investigated in the prospective European Organization for Research and Treatment of Cancer (EORTC) 1634 study (Personalized Risk-Adapted Therapy in Post-Pubertal Patients with Newly Diagnosed Medulloblastoma [PersoMed-I]).

To improve the management of patients with rare cancers, such as medulloblastoma, EURACAN (European Reference Network on Rare Adult Cancers), the European Reference Network for adult rare solid cancers, has been

created with the aim to improve the quality of care for all European citizens. In particular, it seeks to improve patient survival, produce communication tools in all languages for patients and physicians, and develop international databases and tumor banks.

We showed that referring patients to centers with expertise is of utmost importance and is associated with improved survival. Center expertise should be considered as a stratification factor in future clinical trials.

Author contributions

E.F., S.M., A.A.B., and M.M.: first paper draft. All authors contributed to the clinical management of patients included in the study. All authors reviewed the first paper draft and approved the final version of the article.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the Emilia Romagna region (approval number CE 17047) and performed in accordance with national law, institutional ethical standards, and the 1964 Helsinki Declaration and its later amendments.

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