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Original research article

Radiotherapy for adult medulloblastoma: Long term result from a single institution. A review of prognostic factors and why we do need a multi-institutional cooperative program

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ABSTRACT

Aim: We retrospectively analyzed our Institution experience with these patients. The end-points of the analysis were overall survival (OS), disease-free survival (DFS), local control (LC), metastasis free survival (MFS); results were compared with the literature.

Background: Medulloblastoma in adult patients is a very rare disease; the 5 and 10-year overall survival rates range between 33–78% and 27–56%, respectively. The collection of more clinical data is strongly needed.

Materials and methods: From September 1975 to October 2006, we treated 16 adult patients (9 males and 7 females) with a histological diagnosis of medulloblastoma. Acute and late toxicities were scored according to RTOG toxicity scale. Karnofski performance status (KPS) and neurological performance status (NPS) pre- and post-RT were reported.

Median age was 27 years (range 18–53 years). All the patients received cranio-spinal irradiation, two patients were also given chemotherapy. Median follow-up period was 121.5 months.

Results: In January 2014, 10/16 patients were alive without evidence of disease, 6/16 died with progressive disease (1 local and spinal, 3 spinal and 2 extraneural). Ten-year LC, OS, DFS, MFS were, respectively, 84%, 67%, 60% and 59%. Univariate analysis shows that gross total resection is associated with better survival.

No acute or late G3–G4 toxicity was observed.

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Conclusions: This experience and the analysis of the literature confirm the efficacy of post-operative RT but also the need of large datasets to better define prognostic factors and the possible role of the association of chemotherapy.

1. Background

Medulloblastoma (MB) occurs infrequently in adults, with an incidence of 0.5 per million.[1,2] Due to the small number of patients reported in each published series, firm conclusions about the treatment have not yet been reached: in fact, due to the absence of evidence-based prospective studies, treatment modalities for medulloblastoma in adults are too often extrapolated from the available pediatric protocols.

Moreover, since survival results for these patients are relatively good; there is a strong need to define long term toxicities related to the most commonly adopted therapeutic options (i.e., maximal surgical resection and craniospinal irradiation ± adjuvant chemotherapy).

Finally, in more recent years, a relevant research effort has been devoted to the identification of prognostic factors to define a "risk stratification" and possibly contribute to the development of targeted therapies, especially for recurrent or metastatic patients.

In the past, some histologic subtypes of medulloblastoma were already shown to carry a worse prognosis in children, anaplastic/large cell tumors being characterized by a much more aggressive clinical behavior.[3] More recently, multiple medulloblastoma subtypes have been identified with gene expression profiling.[4,5] Interestingly, some of these subtypes are more frequent in adulthood or show a bimodal age distribution: for example, the favorable WNT subtype is more frequent in older children, adolescents, and adults and is associated with a relatively good prognosis, while the "sonic hedgehog" subtype is seen mainly in children less than 3 years old or ("second peak") in teenager/adult patients. Also, this subtype is related in adults with a relatively good prognostic impact, with some exceptions.[5,6]

While the importance of these biomarkers could be elucidated mainly with the accrual of larger prospective datasets, the availability of new reported series could also help by adding to the existing evidence and facilitating the multi-institutional collection of individual patient data, more precisely relating outcome and toxicities to the different therapeutic options and to prognostic and predictive factors than registry-based data.

2. Aim

Our aim is therefore to contribute to the literature by reporting our Institution experience with postoperative treatment of adult medulloblastoma patients.

Retrospective and – even more – prospective cooperative hospital based patient datasets are however strongly needed. Due to a more extensive patient accrual, they could better help to clearly define different prognostic subgroups of patients, possibly to be submitted to treatment protocols characterized by varying degrees of aggressiveness.

3. Materials and methods

We retrospectively analyzed all the adult patients (>18 years old) with a histological diagnosis of medulloblastoma treated at the Istituto del Radio "O.Alberti" – Radiation Oncology Department of the Brescia University (IRA), from September 1975 to October 2006. We considered all the patients who had received surgery and postoperative radiotherapy with radical aim.

The Chang classification has been adopted to re-stage the tumors.[7]

The endpoints considered for analysis were: Overall Survival (OS), defined as the time between the end of the treatment and death; Disease Free Survival (DFS), defined as the time without evidence of disease relapse; Local Control (LC), defined as the time without evidence of relapse in posterior cranial fossa and Metastasis Free Survival (MFS) defined as the time without evidence of distant relapse. All endpoints were calculated from the end of the treatment.

Even with the limit of a small number of patients, univariate analysis was done (Logrank Test) in order to identify factors possibly influencing prognosis (in particular, OS and DFS).

A p-value <0.05 was considered as statistically significant. Statistics were performed with the SPSS software (SPSS Statistics 17.0 © 1993–2007).

The clinical and pathologic features of the cases analyzed are described in Table 1.

To compare the results of our series in terms of outcomes and prognostic factors with those of the literature, we searched the Pub Med database. The articles we judged evaluable are those reported in Table 3.

Table 1 – Characteristics of the population.

Number of patients	16
Median age (range)	27 (18–53)
Male/female (ratio)	9/7
Histology (WHO)[27]	
Classic	8 (50%)
Desmoplastic	8 (50%)
Stage	
High risk (T4/T3b M0, Tx M+)	5
Low risk (T3a/T2/T1 M0)	11

4. Results

From 09/1975 to 10/2006, we treated 16 adult patients (>18 years) with craniospinal radiotherapy. According to Chang classification, 2 patients were classified T1, 6 patients T2, 3 patients T3a, 2 patients T3b and 3 T4. Three patients had leptomeningeal spread at diagnosis. The risk classification is reported in Table 1.

Extent of resection was defined according to postoperative CT or MRI: gross surgical resection (GSR) was defined as the absence of residual tumor on postoperative imaging, partial surgical resection (PSR) as the presence of visible residual tumor. Imaging was performed 60–90 days after surgery. GSR was obtained in 11/16 cases and PSR in 5/16.

All patients received adjuvant radiotherapy with craniospinal irradiation. Radiotherapy was administered using 2D techniques (9/16 patients) or 3D-techniques (7/16 patients). Median doses were 36 Gy (range 23–45 Gy) to the spinal axis, 40 Gy (range 23–46 Gy) to the whole brain and 55.5 Gy (range 40–60 Gy) to the posterior cranial fossa (PCF). Dose per fraction was equal to 1.8 Gy.

Two patients received chemotherapy: one patient (in 1979) received lomustine pre and post radiotherapy and one patient (in 2007) received, in the context of a clinical trial, concomitant vincristine during radiotherapy (1.5 mg/mq/week) followed by VCP for 8 cycles (vincristine 1.5 mg/mq, lomustine (CCNU) 75 mg/mq, cisplatin 70 mg/mq), 1 cycle every 6 weeks (the same patient was treated with 23 Gy on the spinal axis).

No relapses were observed at first follow-up. All of the 5 patients with postoperative residual tumor showed a complete radiological response after radiotherapy.

No patients showed G3–G4 acute or late neurological toxicity, evaluated according to RTOG toxicity scale.[8] Acute neurological toxicity was observed in 5 pts, 3 G1 and 2 G2. Late neurological toxicity was observed in 4 pts, 3 G1 and 1 G2 (mild and moderate headache, 1 patients developed dysmetria). The Karnofsky Performance Status at the first follow-up after radiotherapy was 80 or higher for all the patients.

After a median follow-up of 121.5 months (range 23–433), median OS, LC, DFS and MFS were 121.5, 108, 104.5 and 121 months, respectively.

Five- and 10-year actuarial OS and DFS were equal to 75/67% and 68/60%, respectively. At the time of the analysis 10/16 patients were still alive without evidence of disease, 1/16 was alive with local relapse and spinal progression of disease and 5/16 died for metastatic disease (3/16 with spinal metastasis and 2/16 with progression of medulloblastoma outside CNS).

While disease control at the tumor site of origin was good (5- and 10-year LC rates were equal to 93.8% and 84.4%, respectively), systemic progression rates were found to be relatively high (5-year and 10-year MFS rates of 67.7% and 59.2%, respectively).

We also analyzed (univariate analysis) the effect on survival and local control of potential prognostic factors such as age (<25 vs. >25), gender, histology (classic vs. desmoplastic), surgery (partial removal vs. gross total resection), time interval between surgery and radiotherapy (>3 weeks vs. <3 weeks), chemotherapy (yes vs. no), staging (T1–T3a M0 vs. T3b–T4 M+), involvement of the 4th ventricle and dose to the spinal cord and to the PCF. Gross surgical resection is related with better OS rates (5-year OS rates 92% vs. 40%, $p = 0.05$); since all the patients with postsurgical gross residual tumor were given higher doses (>55 Gy), no clear cut dose–effect relationship was evident (Table 2).

Table 2 – Univariate analysis.

	5-years OS	10-years OS
Whole population (16pts)	75%	67%
Age ($p = 0.176$)		
Age < 25 yrs	100%	83.3%
Age > 25 yrs	55.6%	55.6%
Gender ($p = 0.650$)		
Female	85.7%	61.4%
Male	64.8%	64.8%
Histology ($p = 0.723$)		
Classic	75%	75%
Desmoplastic	72.9%	58.3%
Extent of removal ($p = 0.050$)		
Partial removal	40%	40%
Total removal	92%	78.8%
Interval surgery-RT ($p = 0.230$)		
>3 weeks	78.8%	78.8%
<3 weeks	66.7%	50%
Staging ($p = 0.142$)		
Average risk (T1–T3a M0)	81.8%	81.8%
High risk (T3b–T4 M+)	60%	40%
V4 involvement ($p = 0.094$)		
4th ventricle not involved	80.8%	80.8%
4th ventricle involved	60%	40%

5. Discussion

Table 3 shows the main features of the more relevant series reported in the literature.

The largest retrospective analysis was reported by Lai et al.[9] and includes data on 454 adult medulloblastoma patients identified through the SEER registry from 1973 to 2004. They report 5- and 10-year OS values of 65% and 52%, respectively. At multivariate analysis, diagnosis after 1985, age at diagnosis <20 yrs, gross total resection and craniospinal irradiation were associated with better survival, whereas large cell histology was associated with worse prognosis. Authors underlined that some data, such as Karnofsky performance scores, extent of radiation (craniospinal vs. more limited field), radiation dose and chemotherapeutic treatments were not available. In this study, tumor size, an element of the Chang staging system, was not found to be of prognostic value.

Another large multicenter retrospective study evaluated 253 adult patients with medulloblastoma.[10] treated in France between 1975 and 2004. In this study the median follow up was 7 years and radiotherapy was delivered in 246 patients (142 of them also had chemotherapy). Overall 5 and 10 yrs survival rates of 72% and 55% were reported. At multivariate analysis, brainstem involvement, fourth ventricle floor involvement and dose to posterior fossa <50 Gy had an adverse effect on the

Table 3 – Prognostic factors identified in adult medulloblastoma patients treated with postoperative radiotherapy and their impact on survival.

Study	No. of patients	Survival data	Significant prognostic factors ($p < 0.05$): (u), univariate analysis; (m), multivariate analysis		Notes
			Favorable	Unfavorable	
Friedrich et al.[11] (1998–2009) (prospective study)	70	4 yrs OS 89% 4 yrs EFS 68%		Lateral tumor location (m) Present/unknown residual tumor (m)	Prospective study on M0 MB
Silvani et al.[25] (1991–2001) (prospective study)	28	5 yrs OS 80% 5 yrs PFS 57.6%		Malignant cells in CSF (u)	Prospective study. All patients treated with upfront CDDP+VP16
Lai et al.[16] (1983–2011)	20	3 yrs OS 50% 3 yrs DFS 45%	KPS > 70 (u) Neurologic symptoms duration >30 days (u) Lateral tumor location (u) Standard risk patients (u) RT treatment field (CSI + brain boost) (u) CSI dose > 30 Gy (u)		4/20 adjuvant chemotherapy 1/29 up-front chemotherapy
Balducci et al.[1] (1990–2008)	13	10 yrs OS 76% 10 yrs DFS 84%			2 patients only biopsy + RT +CHT 2 patients received ChT
Ang et al.[28] (1989–2007)	25	5 yrs OS 78% 10 yrs OS 30%			7 patients concomitant CHT 13 patients adjuvant CHT
Riffaud et al.[19] (1977–2005)	27	5 yrs OS 81% 10 yrs OS 62% 5 yrs PFS 72% 10 yrs PFS 57%		Male patients (u) M+ stage (u)	Age ≥ 16 yrs
Ertas et al.[22] (2000–2005)	29	2 yrs PFS 80% 5 yrs PFS 55%	Age < 25 (u)		MB and PNET 11/29 adjuvant CT
Lai et al.[9] (1973–2004)	454	5 yrs OS 69.4% 10 yrs OS 52.1%	Age at diagnosis < 20 yrs (m) Diagnoses after 1980 (m) Gross total resection (m) Postoperative RT (m)	Large cell histology (m)	SEER database study

Table 3 (*Continued*)

Study	No. of patients	Survival data	Significant prognostic factors ($p < 0.05$): (u), univariate analysis; (m), multivariate analysis		Notes
			Favorable	Unfavorable	
Padovani et al.[10] (1975–2004)	253	5 yrs OS 72% 10 yrs OS 55%		High risk population (metastatic disease, partial surgery. CSF involvement) (u) Metastasis (u) Postsurgical performance status ≥ 3 (u) V4 floor involvement (u) Dose to spinal cord < 29 Gy (u) Dose to PCF < 50 Gy (u) Brainstem involvement (m) Floor of fourth ventricle involvement (m) Dose to the PCF < 50 Gy (m)	Multicenter retrospective study
Brandes et al.[24] (1989–2001) (prospective study)	36	5 yrs OS 75% 5 yrs PFS 72%			Prospective phase II study 26/36 (high risk patients) RT + CHT
Abacioglu et al.[18] (1983–2000)	30	5 yrs OS 65% 8 yrs OS 51% 5 yrs PFS 63% 8 yrs PFS 50%		M+ stage (u) Interval surgery/RT > 6 w (u)	Age ≥ 16
Chan et al.[12] (1986–1996)	32	5 yrs OS 83% 8 yrs OS 45% 5 yrs PFS 57% 8 yrs PFS 40%	Gross total resection (u)		Age ≥ 16
Le et al.[20] (1970–1994)	34	5 yrs OS 58% 5 yrs PFS 61%	Older patients (m) Female patients (m) Localized disease (m)		Age ≥ 15 yrs
Carrie et al.[17] (1975–1991)	156	5 yrs PFS 61% 10 yrs PFS 48%	Postsurgical performance status < 2 (m) Desmoplastic type (m) Spinal axis dose > 30 Gy (m)	Floor of fourth ventricle involvement (m)	Histological retrospective study

Table 3 (*Continued*)

Study	No. of patients	Survival data	Significant prognostic factors ($p < 0.05$): (u), univariate analysis; (m), multivariate analysis		Notes
			Favorable	Unfavorable	
Giordana et al.[23] (1977–1990)	44	5 yrs OS 40% 10 yrs OS 35.6%	Age < 37 yrs (u) Radiotherapy (dose 50–55 Gy on PCF and 30–36 Gy on spinal axis) (u)		
Carrie et al.[13] (1975–1990)	30	5 yrs OS 58.5% 10 yrs OS 41%		Malignant cells in CSF (u) Brain stem invasion (u) Cerebellar peduncle infiltration (u) Partial surgery (u) Postoperative Performance Status > 2 (u)	28 pts received RT 23 pts received ChT
Chargari et al.[14]	36	3 yrs OS 67.3% 3 yrs PFS 57.4%	Gross total resection (u)	High risk population (u)	11/36 pts only postoperative RT 25/36 high-risk pts RT + CHT
Hartsell et al.[15] (1969–1986)	17	5 yrs OS 81.3% 5 yrs PFS 63.1%		Partial resection (u) Classical histology (u)	
Haie et al.[21] (1961–1982)	20	5 yrs OS 78% 10 yrs OS 55%	Male patients (u)		Age ≥ 16
Prados et al.[29]	47	5 yrs OS (good risk) 81% 5 yrs OS (poor risk) 54%		"Poor risk" (partial removal, metastatic disease, brainstem or leptomeningeal invasion) (u)	142 patients treated with RT+ CHT
Our study (1975–2006)	16	10 yrs OS 67% 10 yrs DFS 60.2%	Gross total resection (u)		

event free survival in the entire series, whereas dose to the posterior fossa <50 Gy and fourth ventricle floor involvement only were associated with a worse OS in the standard-risk group.

At our knowledge, patients with metastatic disease at presentation have a worse prognosis. Despite that, many authors have found other important prognostic factors that could influence prognosis such as the extent of resection,[9–15] the lateral tumor location[11,16] and the invasion of the brain stem.[10,16,17] In many studies partial surgery is one of the inclusion criteria for "high risk classification" patients along with the presence of metastasis and/or T3b/T4 according to Chang staging. Some minor prognostic factors have been also reported, but not by all the authors: for example the interval between surgery and RT[18] or the postoperative performance status.[10,13] Some others, such as sex[19–21] and age[9,20,22,23] are clearly controversial. In our study, histology did not prove to be a prognostic factor: in many of the studies reported, a high frequency of desmoplastic variant of medulloblastoma was observed (the adult age represents the second peak age

incidence after the early childhood), but it does not influence prognosis, except in a few series.[15,17]

It is still unclear if chemotherapy could be useful for adult patients with medulloblastoma.

In the prospective study by Brandes et al.,[24] in which 36 patients were recruited from 1989 to 2001, a 5-year OS and PFS rates of 75% and 72%, respectively, were reported. In this study, the outcome of low risk patients treated with postoperative radiotherapy alone is compared with that of high risk patients treated with 2 cycles of upfront chemotherapy followed by radiotherapy and adjuvant chemotherapy: no differences were found between the two groups, suggesting that adult average-risk patients may also profit from chemotherapy.

Another Italian prospective study[25] published in 2011 included 28 adult patients treated between 1991 and 2001 with surgery, 3 cycles of upfront chemotherapy with cisplatinum and VP16 followed by craniospinal radiotherapy. Compared to Brandes et al., in this study the patients were treated with the same schedule (CHT + RT) irrespective of their risk class. Of 28 patients, 18 developed a first recurrence. The authors concluded that the upfront chemotherapy regimen was tolerated (but 14% experienced leukopenia and thrombocytopenia grade 4), but did not ameliorate the results of craniospinal RT; therefore, the role of combination administration of CDDP and VP16 started before radiotherapy in reducing recurrences remains unclear.

In 2012, Friedrich et al.[11] published a prospective study in which they followed seventy adult patients with non-metastatic medulloblastoma treated with postoperative radiotherapy (35.2 Gy on the spinal axis with a boost of up to 55.2 Gy to the posterior fossa) followed, for 49 of these patients, by chemotherapy with CCNU, vincristine and cisplatin according to a pediatric protocol.[26] They concluded that chemotherapy is feasible in adult patients as far as toxicity is concerned, but they did not find any prognostic difference between the groups treated with or without chemotherapy. They also found that lateral tumor location (more common in adults than in children) and incompletely resected tumor are related to worse EFS rates.

According to this study, the main site of relapse, as in other studies,[10,12,17,18] was the posterior fossa. This data is not confirmed in our population (only 1/16 patients experienced local relapse). A higher incidence of extraneural metastases has been reported in adults, when compared to children.[12,18,19] In our study, one patient developed scapular and pelvic bone metastases and another had a histologically confirmed oropharingeal relapse.

Survival data in our study are similar to those presented in the literature and confirm the key role of a complete surgical removal and of postoperative radiotherapy in these patients.[9,11,23]

6. Conclusions

Medulloblastoma in adults is a very rare disease and treatment strategies (often derived from pediatric protocols) are still not completely clear.

Surgery as complete as safely feasible and postoperative radiotherapy is the cornerstones of medulloblastoma treatment in adults. In recent years, reported results with craniospinal radiotherapy alone have been relatively good, but patients with unfavorable prognostic factors seem to need a more aggressive treatment, due to significantly worse survival. Chemotherapy results in these patients are controversial and the role of maintenance or up-front chemotherapy to improve survival still not clear. The use of targeted therapies guided by the newer biomarkers could be a promising research pathway.[30]

However, due to the rarity of the disease, no mono-institutional experience seems to be sufficient by itself to answer these questions and the compilation and analysis of multi-institutional prospective or retrospective multi-institutional hospital based pooled collections of individual patient data could help, providing a more precise information than that provided by registries like SEER.[9]

Conflict of interest

None declared.

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