Neurological Sciences
https://doi.org/10.1007/s10072-020-04556-6

ORIGINAL ARTICLE

Medulloblastoma of the adult: results from a multicenter retrospective study by AINO (Italian Association of Neuro-Oncology) and SIN (Italian Society of Neurology)

Paola Gaviani[1] · Giorgia Simonetti[1] · Roberta Rudà[2] · Federica Franchino[2] · Giuseppe Lombardi[3] · Marco Possanzini[4] · Sara Squintu[4] · Veronica Villani[5] · Mariaausilia Teriaca[6] · Francesco Cavallieri[7] · Maria Caffo[8] · Andrea Salmaggi[9] · Andrea Bianco[10] · Elena Anghileri[11] · Mariangela Farinotti[12] · Irene Tramacere[13] · Antonio Silvani[1]

Received: 7 April 2020 / Accepted: 2 July 2020

Abstract

Introduction Medulloblastoma (MB) is the most common primary malignant intracranial tumor in childhood, but it is very rare in adults, and for this reason, the optimal treatment has not yet been defined. We designed a multicentric study in order to define relevant outcome measures for future prospective studies.

Materials and methods The project involved 10 Italian centers. The database shared among the centers contains epidemiological, diagnostic (radiological and histological/molecular), therapeutic, recurrence information, and survival data.

Results A total of 152 patients (102 males and 50 females, median age 32) were included in the study. Twenty-three of 152 patients had a diagnosis of classic medulloblastoma, 52/152 had desmoplastic/extensive nodularity, 2/152 had large-cell anaplastic medulloblastoma, and the remaining had diagnoses not otherwise specified. Almost all patients underwent craniospinal irradiation after surgery; in 85.5% of patients, adjuvant chemotherapy, mainly platinum- and etoposide-based chemotherapy, was performed immediately after RT. Upon recurrence, most patients were retreated with various chemotherapy regimens, including intrathecal chemotherapy in patients with leptomeningeal dissemination. The overall survival (OS) rate at 5 years was 73.3% (95% CI, 65.0–80.0%). The median OS for the whole group of patients was 112 months.

Conclusions The data collected were mainly consistent with the literature. A limitation of this study was the large number of patients lost to follow-up and the lack of molecular data for most patients diagnosed until 2010. An important challenge for the future will be MB biologic characterization in adults, with the identification of specific genetic patterns. It will be important to have more national and international collaborations to provide evidence-based management strategies that attempt to obtain a standard of care.

Keywords Adult medulloblastoma · Chemotherapy · Radiotherapy · Survival · Database

✉ Giorgia Simonetti
giorgia.simonetti@istituto-besta.it

[1] Neuro-oncology Unit, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Celoria, 11, 20133 Milan, Italy

[2] Department of Neuro-Oncology, University of Turin and City of Health and Science University Hospital, Turin, Italy

[3] Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

[4] Radiotherapy Department, Businco Oncological Hospital, Cagliari, Italy

[5] Neuro-Oncology Unit, Regina Elena Cancer Institute, Rome, Italy

[6] Department of Experimental and Clinical Biomedical Sciences, Radiation Oncology Unit, University of Florence, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

[7] Neurology Unit, Neuromotor & Rehabilitation Department, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy

[8] Department of Neurosurgery, University of Messina, Messina, Italy

[9] Neurological Department, ASST, Lecco, Italy

[10] Neurosurgery "Maggiore della Carità" University Hospital, Corso Mazzini 18, 28100 Novara, Italy

[11] Neurology VIII-Molecular Neuro-Oncology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Celoria, 11, 20133 Milan, Italy

[12] Unit of Neuroepidemiology, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy

[13] Department of Research and Clinical Development, Scientific Directorate, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Celoria, 11, 20133 Milan, Italy

Published online: 11 July 2020

Introduction

Medulloblastoma (MB) is a highly malignant central nervous system (CNS) tumor that arises from the cerebellum; it represents the most common primary malignant intracranial childhood neoplasm, accounting for 15 to 30% of all childhood brain tumors; however, it is a very rare tumor in adults, with an incidence on the order of 0.6–1 cases/million, and 80% of cases occur before the end of the fourth decade [1]. Due to the small number of adult patients, reports of adults with MB are limited to retrospective series of single-institution trials, and few prospective studies have been performed. Maximal safe surgical resection remains the cornerstone of therapy for MB. However, surgery alone produces unacceptably high recurrence rates and dismal survival in MB, needing adjuvant radiation, which has been considered an integral part of the management of patients with MB. The question of whether adults require different treatments than children remains relatively unanswered. Several authors have suggested that adult and childhood MB are two different diseases with both phenotypic and clinical differences. Until now, adult patients have commonly been treated with the same therapies that were developed for children, and the optimal treatment for adults with newly diagnosed MB has not been defined. If we compare the scenario between adult and pediatric medulloblastoma patients, we face two very different situations. Pediatric neuro-oncologists have a strong net with some important hubs, treating a large number of patients. These groups are very active, with several national and international studies and consensus groups. This is not quite the case with adult patients. In recent years, only a few Italian groups have reported small series [2–5]. Therefore, we designed a multicentric study on behalf of the Italian Association of Neuro-Oncology (AINO) and Italian Society of Neurology (SIN), involving multiple centers in Italy, with the development of a complete database shared among the centers that contains epidemiological, diagnostic (radiological and histological/molecular), first-line radiochemotherapy, and recurrence information as well as survival data from adult medulloblastoma patients. The primary aim of this study was to describe the clinical (including surgical procedure, radiotherapy and chemotherapy), radiological, and molecular features of a large population of adult medulloblastoma patients diagnosed between 2000 and 2018. Such collection was retrospectively acquired in a "real-life" setting with the purpose of identify relevant outcome measures for future prospective studies. The secondary aim was to evaluate survival time.

Methods

In this multicenter retrospective observational study, we collected clinical and radiological data from medulloblastoma patients. The study was first proposed by the AINO and subsequently extended to the SIN Neuro-Oncology Group. The Neuro-Oncology Unit of the National Neurological Institute "Carlo Besta" in Milan was designated as the coordinating center. Any clinical center willing to participate in the national network was included whenever a minimum of two complete cases were provided. Records were collected on a common web-based platform (Microsoft Excel) that was customized for this study and accessible only with a password. Each included patient was labeled with a unique code to warrant anonymity. The database, shared among the centers, contained epidemiological, diagnostic (radiological and histological/molecular), therapeutic, and recurrence information, as well as survival data. We collected follow-up data from 2000 to 2018. The study was closed at the end of June 2018 (minimum follow-up of 30 months). We included information on the symptoms at onset, radiological features, molecular biology pattern, and treatments performed. Such data were used to assess whether real-life clinical practice was homogeneous among centers throughout the national territory. In addition, we obtained information on the use of treatment regimens.

Histological diagnosis of MB was made by a local pathologist/neuropathologist, assessing the desmoplastic (nodular) type, classic type, "extensive nodularity," and "large-cell" phenotypes according to WHO criteria. There is also a poorly defined subgroup MB, called "not otherwise specified" (NOS).

Extent of resection was defined on the basis of postoperative imaging as gross/near total resection (no residual tumor or tumor < 1.5 cm^2), subtotal/partial resection (≥ 1.5 cm^2 tumor remaining), and biopsy [6].

At the time of relapse, we named "recurrence" a regrowth of tumor in patients who underwent a gross/near total resection at first surgery and "progression" a growth of residual tumor not completely removed at first surgery.

Survival time from surgery to progression, death, or the last date of follow-up was measured and estimated by the Kaplan–Meier method [7]; 95% confidence intervals were calculated using the associated estimated standard errors. The log-rank test was used to compare the significance of the following prognostic variables: type of surgery (gross total resection vs partial resection/biopsy) and histological subtype. STATA statistical software, version 16 (StataCorp. 2019, Stata Statistical Software: Release 16, College Station, TX: StataCorp LLC), was used for the statistical analysis.

Treatment toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The study was conducted according to the ethical rules for retrospective observational studies and was approved by the ethical committee of the coordinating center and subsequently by each local committee of the centers in the network. Each participating hospital retained the personal data of their

patients, and each local investigator acted as a controller. Data were decodable only in each single participating clinical center. Data access for analysis was granted to the principal investigator of the study (AS) and to his direct collaborators, who were bound to respect confidentiality rules.

Results

The project involved 10 Italian centers with a total of 152 collected patients (102 males and 50 females) included in the study. The median age at diagnosis was 32 years (18–85). The most frequent symptoms at onset were headache (48% of patients), ataxia (31% of patients), cranial nerve palsies (12% of patients), and motor or sensory deficits (9% of patients). Tumors were localized mainly in the cerebellar hemispheres, accounting for 65% of cases; in 30% of patients, tumors were located in the vermis or the fourth ventricle; and in 5% of patients, tumors were located in the cerebellopontine angle. In 9.1% of patients, MRI and spinal fluid were suggestive of neoplastic dissemination at diagnosis.

All patients underwent surgery at the time of diagnosis, including biopsy in 7/152 patients and partial exeresis in 58/152 patients; gross total resection, as defined by postoperative contrast-enhanced cranial MRI, was achieved in 87/152 patients. A total of 18/152 patients had hydrocephalus at diagnosis, and these patients underwent ventriculoperitoneal shunt placement before tumor resection. Concerning tumor histology, 23/152 patients had a diagnosis of classic medulloblastoma, 52/152 desmoplastic/nodular (DNMB), and 2/152 large cell/anaplastic (LC/A), and in the other 75/152 patients, the diagnosis was not otherwise specified (NOS). Genetic profiles were available in 64% of patients, but in the majority, this profile was not complete (Table 1).

Regarding treatments, almost all patients (96.7%) underwent craniospinal fractionated external-beam radiotherapy (EBRT). A dose of 30 Gy with 1.8 Gy/fraction/day was prescribed to low risk patients (8.5% of patients), while 36 Gy was prescribed in the other patients. The posterior fossa was boosted with variable dosage (range 18 to 56 Gy).

Overall, a median total dose for craniospinal + posterior fossa boost was 54–56 Gy.

Only in 8/152 patients, radiotherapy was not performed due to clinical conditions (KPS < 60) or age > 80 years.

Concerning radiation therapy-related toxicity, no patient interrupted the treatment due to acute toxicity as cerebral edema or dermatitis or fatigue. Unfortunately, the characteristics of the retrospective database did not allow to evaluate long-term cognitive, endocrinological, hormonal, and auditory sequelae.

The patients were retrospectively stratified into standard and high-risk groups according to clinicopathological variables pertaining to age, presence of metastases, extent of resection, histological subtypes, and genetic alterations, when available. In 86% of patients, adjuvant chemotherapy, mainly platinum- and etoposide-based chemotherapy, was performed immediately after RT; in a relatively small percentage of patients (8.5%) considered low-risk patients, chemotherapy was not performed at diagnosis. The observed toxicity of cisplatinum/etoposide chemotherapy was mainly hematological, with leukopenia and thrombocytopenia (14% with grade 4). Patients with leptomeningeal dissemination at diagnosis and a good performance status underwent intrathecal therapy, mainly consisting of liposomal cytarabine; other treatments included oral temozolomide and intrathecal methotrexate.

Chemotherapy toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Concerning the patients who received chemotherapy, 20% reported grade 3–4 myelotoxicity, including cases of leukopenia, thrombocytopenia, and fatigue and oral mucositis in one case.

The most common site of recurrence/progression was the posterior fossa. In fact, in approximately 50% of patients, it was the unique site of relapse. In the remaining percentage of patients, recurrence/progression was multifocal including not only posterior fossa but also additional central nervous system

Table 1 Baseline of patients' characteristics

Number of patients	152
Median age (range)	32 (18–85)
Gender	
Male	67.1%
Female	32.8%
Symptoms	
Headache	48%
Ataxia	31%
Cranial nerve alterations	12%
Motor/sensory hemisyndrome	9%
Tumor localization	
Cerebellar hemispheres	65%
Vermis/fourth ventricle	30%
Cerebellopontine angle	5%
Type of surgery	
Gross total resection	57.2%
Partial resection	38.1%
Biopsy	4.6%
Histologic diagnosis	
Classic medulloblastoma	15.1%
Desmoplastic/nodular (DNMB)	34.2%
Large cell/anaplastic (LC/A)	1.3%
Not otherwise specified (NOS)	49.3%

(CNS) sites such as supratentorial region and brain stem region. Leptomeningeal dissemination (nodular or linear disease) and distant extra CNS metastases (gross bone and lymph nodes) were seen in 14% of patients.

At the time of first recurrence, the treatment was not homogeneous. In patients with local recurrence, a second surgery was performed in about 30% of patients. A reirradiation, mainly consisting of radiosurgery, was performed in 6% of patients. Most patients were retreated with various chemotherapy regimens, including rechallenge with platinum and/or etoposide (83%), carboplatin (6%), nitrosourea-based PCV (2%), and cyclophosphamide (2%). A small group of patients (8%) was treated with oral temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle) for a maximum of 6 cycles.

At the time of a second or subsequent recurrences, 44% of patients were able to receive at least another line of chemotherapy mainly oral (temozolomide or etoposide), and in a small percentage of patients (4%), a combination of cisplatin, vincristine, and CCNU. Moreover, three patients were included in experimental clinical trials with sonic hedgehog pathway inhibitors.

We collected follow-up data from 2000 to 2018. At the time of data analysis, 64 deaths (42% of patients) had occurred.

Among the whole group of patients, the median PFS was 22.8 months (2–97.3 months).

Median OS for the whole group of patients was 112 months (95% CI 95–168) (Fig. 1). OS rate at 12 months was 94% (95% CI, 88.8–96.8%) and OS rate at 5 years was 73.3% (95% CI, 65.0–80.0%). The extent of surgery (gross total resection vs partial resection/biopsy) did not achieve statistical significance ($p = 0.08$) (Fig. 2). Concerning tumor histology, there were no statistically significant differences between classic medulloblastoma, DNMB, LC/A, and NOS ($p = 0.22$) (Fig. 3).

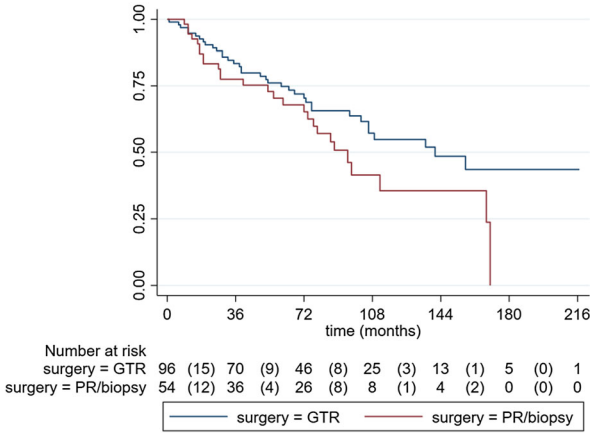

Fig. 2 Survival for gross total resection vs partial resection/biopsy

Discussion

Medulloblastoma is the most frequent primary malignant brain tumor (WHO grade IV) in children, but it is very rare in adults, and often, survival rates and prognostic factors for adult MB are difficult to assess due to the scarcity of information. The 5-year overall survival rates in adult patients treated with craniospinal radiotherapy range from 58 to 76%. Furthermore, the median survival time ranges widely from 6 to 17.6 years [8, 9]. To date, there has been a lack of data to guide adjuvant treatment decision-making for MB in adults due to the relative rarity of the disease in adults compared with the pediatric population [10]. We created an online web database for rare tumors of the CNS. We decided to start our work with medulloblastoma as an example of multidisciplinary treatment for a rare tumor without strong codified guidelines. Initially, to simplify data collection, we chose to include in the database only the patients treated over the past 5 years; then, the period was extended to the past 18 years. We gained inspiration from a paper published in JNO in 2014 [11]. This retrospective, multicentric study, involving 10 Italian centers,

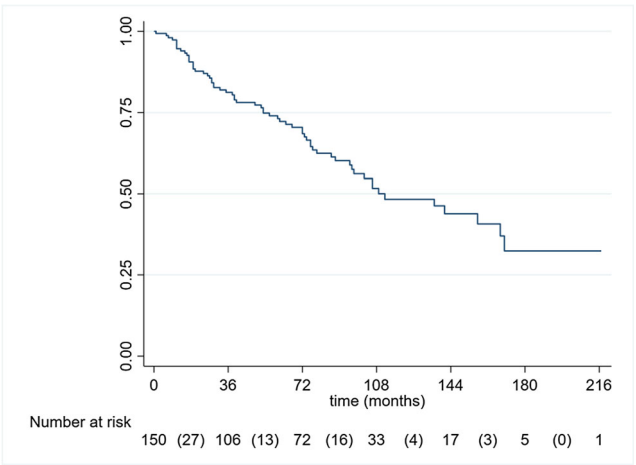

Fig. 1 Overall survival of the cohort

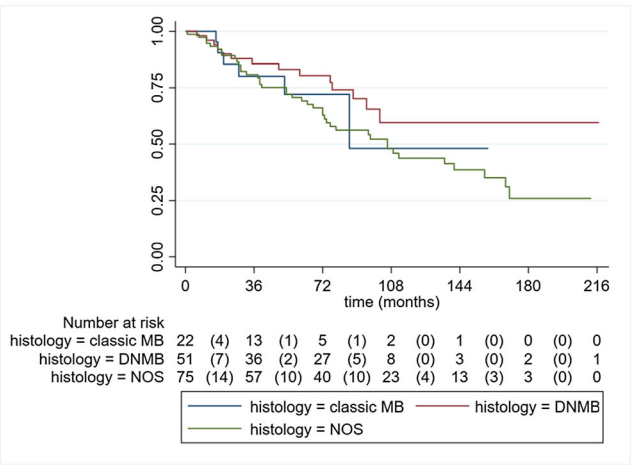

Fig. 3 Effect of histology on overall survival

aimed to describe the clinical, epidemiological, and treatment data regarding adult medulloblastoma in an updateable database to acquire new knowledge about the disease and clinical management.

Although considering the rarity of the disease, the study allowed to collect the largest national recent series of adult medulloblastoma. Moreover, thanks to the high number of the centers of expertise involved, a significantly higher quality of the data has been obtained with respect to conventional mono-institutional studies.

From a therapeutic point of view, maximal surgery has been established as the cornerstone of therapy. Several series have established complete surgical resection as the most important prognostic factor [12, 13]. Our study confirmed this belief: all patients underwent surgery at diagnosis, with a biopsy performed in only 4.6% of patients, with almost all due to high-risk tumor localization or the poor clinical conditions of patients. However, our data showed a trend, but not a statistically significant difference in survival between gross total resection vs partial resection/biopsy with a median OS of 141 months vs 95 months ($p = 0.08$).

Adjuvant radiation therapy has been considered an integral part of the management of patients with MB [14]. Craniospinal irradiation is always recommended to prevent tumor recurrence, even in cases of total tumor removal. The conventional doses of radiotherapy are approximately 36 Gy in the craniospinal axis plus a boost of 18–20 Gy in the posterior fossa (PF) (total dose of 54–56 Gy). The high propensity for CSF dissemination makes it necessary to treat the entire neuraxis with an adequate dose of radiation followed by a boost to the PF. A crucial point in the treatment plan is the usage of total doses of radiation delivered to the PF. Several papers have reported this site with doses of RT greater than 50 Gy as a positive prognostic factor [15]. In our experience, almost all patients underwent craniospinal irradiation at a dose of 36 Gy with a boost on the PF following surgery; in only 5.2% of patients, radiotherapy was not performed due to clinical conditions or age > 80 years.

The real benefit of chemotherapy in adults is not clear. Moreover, in earlier series of patients, both chemotherapy and radiotherapy treatments were heterogeneous in the treatment schedules and evaluations of responses. Several institutional studies reporting on adult MB have suggested a survival benefit of adjuvant chemotherapy, while others have not [16]. Recommendations by EANO-EURACAN suggest that adult medulloblastoma patients should all receive chemotherapy, despite their risk class; however, these recommendations are mostly derived from experience in the pediatric population and on single-arm prospective trials in adults and are level II.

Due to the very low incidence of these tumors, few prospective studies have been performed, and the large amount of data from the few retrospective series represents a potential bias in analysis. A prospective study on adult MB investigated the effect of radiotherapy alone for standard-risk patients and upfront chemotherapy followed by radiotherapy and adjuvant chemotherapy for high-risk patients and found 5-year overall survival rates of 80% and 73% and 5-year progression-free survival rates of 80% and 69%, respectively [3]. The prospective NOA-07 study investigated a combination of resection, chemoradiotherapy with vincristine, and sequential chemotherapy with vincristine/cisplatin/lomustine in adult medulloblastoma patients [17]. The study showed that the combination of radiochemotherapy followed by maintenance chemotherapy with cisplatin, lomustine, and vincristine was more toxic in adults than in children. A large retrospective study by Padovani et al. demonstrated no survival benefit from the addition of adjuvant chemotherapy ($n = 253$) [18]. On the other hand, a considerable retrospective analysis of a national database by Benjamin H. Kann et al. demonstrated that the combination of postoperative chemotherapy and radiotherapy compared with radiotherapy alone was associated with superior survival in adult MB patients [19].

Our study showed that in high-risk patients, adjuvant chemotherapy was performed immediately after RT and was preferentially administered in patients with residual disease or CSF positivity, while in patients considered low risk, chemotherapy was not performed at diagnosis but only at the time of recurrence; the chemotherapy administered mainly consisted of platinum- and etoposide-based chemotherapies. The assessment of "high"- vs "low"-risk groups in this study was particularly challenging because in this database, we collected patient data from 2000 to 2018, and a complete genetic profile was available only in a small percentage of patients; in fact, the 2016 World Health Organization (WHO) classification developed a combination of histological criteria entities and genetically defined groups with the intent to stratify patients with low and high risk. In particular, the 2016 WHO classification developed this further to a combination of histological criteria with classic (60–70% in adults), desmoplastic/nodular (25–40%), extensive nodular (< 5%), and large cell/anaplastic (10–25%) entities and genetically defined groups. Four genetic subgroups (wingless [WNT], sonic hedgehog [SHH], group 3, and group 4) defined by expression patterns and epigenetic signatures allow for reliable prognostication. Patients with MYC/MYCN amplification and p53 mutation have a worse prognosis. In adults, group 3 does not virtually exist [20, 21]. Thus, a strong limitation of our database was the low number of genetic investigations available. This is partially due to the retrospective nature of the study, which included patients since 2000. Moreover, in some centers, these investigations were not routinely performed. In centers where the number of cases was low, it was difficult to organize all the methods and tools necessary for modern integrated diagnosis and high-level molecular analysis, confirming the need to identify few high-volume centers with all the available facilities to optimize diagnosis and management of these are tumors.

The tolerance of chemotherapy is a significant issue that should not be ignored in the clinical management of adult medulloblastoma patients. In the literature, chemotherapy seems indeed to be more toxic in adults than in children. Friedrich et al. [22] reported an incidence of grade C3 hematological toxicity in adult patients treated with a regimen of CCNU, vincristine, and cisplatin for eight cycles after RT of 58%. In our study, the incidence of grade 3–4 leukopenia was 20% in patients receiving chemotherapy treatment mostly consisting of a regimen of cisplatin, etoposide, vincristine, and lomustine, and the toxicity was mainly due to the nitrosourea regimen.

A tendency to avoid chemotherapy in patients receiving high-dose craniospinal irradiation (CSI) compared with low-dose CSI was not found in our study. Almost all patients who underwent CSI also received chemotherapy unless they had a poor performance status.

Finally, nonhematological toxicities such as polyneuropathy and hearing loss deficits were not collected or described from most centers; moreover, data regarding returning to work as well as fertility status after treatments were not collected.

The optimal treatment for local relapse remains controversial, and no randomized controlled trials are available. A number of chemotherapy regimens (with or without high-dose chemotherapy) have been proposed. Several clinical practice guidelines recommend maximal safe second surgery at relapse [10]. In our experience, a few patients with local relapse without signs of leptomeningeal dissemination underwent repeat surgery and/or radiosurgery STR, and reirradiation was feasible and safe without evidence of acute or late toxicity. Moreover, at the time of recurrence, different chemotherapy agents were used, confirming data from the literature; a relatively significant number of patients were treated with temozolomide. One patient was treated with high-dose multiagent chemotherapy followed by bone marrow "rescue."

From a prognostic point of view, our data are quite congruent with the literature. In particular, the lack of prognostic significance between desmoplastic and classic medulloblastoma is in line with data from large patient series. Finally, in our series, gross total resection seems to correlate with better survival compared with partial resection or biopsy; however, this data is not statistically significant.

Conclusion

The data collected on patients and their disease features were mainly in line with the literature. A limitation of this retrospective study was the large number of patients lost at follow-up and the lack of molecular data for most patients diagnosed until 2010. An important challenge for the future will be the biologic characterization of adults MB, with the identification of specific genetic patterns that could be important for prognosis and possible target therapies. It will be important to have more active national and international collaboration to provide evidence-based management strategies that attempt to obtain a standard of care in adult MB. In conclusion, our study collects one of the largest adult MB populations providing a snapshot of the relevant outcome measures that should be included in prospective studies. Future studies should be designed on standards of imaging and pathology through the centralization of data.

In addition, endocrinology and fertility data as well as secondary tumor susceptibility and quality of life will contribute to improving the quality of information.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study has been approved by the Ethics Committee of the IRCCS Istituto Neurologico Carlo Besta.

References

1. Smoll NR, Drummond KJ et al (2012) The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children. J Clin Neurosci 19(11):1541–1544
2. Silvani A, Gaviani P, Lamperti E, Botturi A, DiMeco F, Franzini A, Ferroli P, Fariselli L, Milanesi I, Erbetta A, Pollo B, Salmaggi A (2012) Adult medulloblastoma: multiagent chemotherapy with cisplatinum and etoposide: a single institutional experience. J Neuro-Oncol 106(3):595–600
3. Brandes AA, Franceschi E, Tosoni A, Blatt V, Ermani M (2007) Long-term results of a prospective study on the treatment of medulloblastoma in adults. Cancer 110(9):2035–2041
4. Buglione M, Ghirardelli P, Triggiani L, Pedretti S, Pasinetti N, de Bari B, Tonoli S, Borghetti P, Spiazzi L, Magrini SM (2015) 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. Rep Pract Oncol Radiother 20(4):284–291
5. Balducci M, Chiesa S, Chieffo D et al (2012) The role of radiotherapy in adult medulloblastoma: long-term single-institution experience and a review of the literature. J Neuro-Oncol 106(2):315–323
6. Thompson EM, Hielscher T, Bouffet E, Remke M, Luu B, Gururangan S, McLendon RE, Bigner DD, Lipp ES, Perreault S, Cho YJ, Grant G, Kim SK, Lee JY, Rao AAN, Giannini C, Li KKW, Ng HK, Yao Y, Kumabe T, Tominaga T, Grajkowska WA, Perek-Polnik M, Low DCY, Seow WT, Chang KTE, Mora J, Pollack IF, Hamilton RL, Leary S, Moore AS, Ingram WJ, Hallahan AR, Jouvet A, Fèvre-Montange M, Vasiljevic A, Faure-Conter C, Shofuda T, Kagawa N, Hashimoto N, Jabado N, Weil AG, Gayden T, Wataya T, Shalaby T, Grotzer M, Zitterbart K, Sterba J, Kren L, Hortobágyi T, Klekner A, László B, Pócza T, Hauser P, Schüller U, Jung S, Jang WY, French PJ, Kros JM, van Veelen MLC, Massimi L, Leonard JR, Rubin JB, Vibhakar R, Chambless LB, Cooper MK, Thompson RC, Faria CC, Carvalho A, Nunes S, Pimentel J, Fan X, Muraszko KM, López-Aguilar E, Lyden D, Garzia L, Shih DJH, Kijima N, Schneider C, Adamski J,

Northcott PA, Kool M, Jones DTW, Chan JA, Nikolic A, Garre ML, van Meir EG, Osuka S, Olson JJ, Jahangiri A, Castro BA, Gupta N, Weiss WA, Moxon-Emre I, Mabbott DJ, Lassaletta A, Hawkins CE, Tabori U, Drake J, Kulkarni A, Dirks P, Rutka JT, Korshunov A, Pfister SM, Packer RJ, Ramaswamy V, Taylor MD (2016) Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. Lancet Oncol 17(4):484–495

7. Bland JM (1998) Survival probabilities (the Kaplan-Meier method). BMJ 317(7172):1572–1580
8. Majd N, Penas-Prado M et al (2019) Updates on management of adult medulloblastoma. Curr Treat Options in Oncol 20(8):64
9. Atalar B, Ozsahin M, Call J, Napieralska A, Kamer S, Villa S, Erpolat P, Negretti L, Lassen-Ramshad Y, Onal C, Akyurek S, Ugurluer G, Baumert BG, Servagi-Vernat S, Miller RC, Ozyar E, Sio TT (2018) Treatment outcome and prognostic factors for adult patients with medulloblastoma: the Rare Cancer Network (RCN) experience. Radiother Oncol 127(1):96–102
10. Franceschi E, Hofer S, Brandes AA, Frappaz D, Kortmann RD, Bromberg J, Dangouloff-Ros V, Boddaert N, Hattingen E, Wiestler B, Clifford SC, Figarella-Branger D, Giangaspero F, Haberler C, Pietsch T, Pajtler KW, Pfister SM, Guzman R, Stummer W, Combs SE, Seidel C, Beier D, McCabe MG, Grotzer M, Laigle-Donadey F, Stücklin ASG, Idbaih A, Preusser M, van den Bent M, Weller M, Hau P (2019) EANO-EURACAN clinical practice guideline for diagnosis, treatment, and follow-up of postpubertal and adult patients with medulloblastoma. Lancet Oncol 20(12):e715–ee72
11. Cosman R, Brown CS, DeBraganca KC et al (2014) Patterns of care in adult medulloblastoma: results of an international online survey. J Neuro-Oncol 120(1):125–129
12. Trinh VT, Davies JM, Berger MS et al (2015) Surgery for primary supratentorial brain tumors in the United States, 2000-2009: effect of provider and hospital caseload on complication rates. Neurosurg. 122(2):280–296
13. Long DM, Gordon T, Bowman H et al (2003) Outcome and cost of craniotomy performed to treat tumors in regional academic referral centers. Long DM Neurosurg 52(5):1056–1063
14. De B, Beal K, De Braganca KC et al (2018) Long-term outcomes of adult medulloblastoma patients treated with radiotherapy. J Neuro-Oncol 136(1):95–104
15. Abacioglu U, Uzel O, Sengoz M, Turkan S, Ober A (2002) Medulloblastoma in adults: treatment results and prognostic factors. Int J Radiat Oncol Biol Phys 54(3):855–860
16. Franceschi E, Bartolotti M, Paccapelo A, Marucci G, Agati R, Volpin L, Danieli D, Ghimenton C, Gardiman MP, Sturiale C, Poggi R, Mascarin M, Balestrini D, Masotto B, Brandes AA (2016) Adjuvant chemotherapy in adult medulloblastoma: is it an option for average-risk patients? J Neuro-Oncol 128(2):235–240
17. Beier D, Proescholdt M, Reinert C, Pietsch T, Jones DTW, Pfister SM, Hattingen E, Seidel C, Dirven L, Luerding R, Reijneveld J, Warmuth-Metz M, Bonsanto M, Bremer M, Combs SE, Rieken S, Herrlinger U, Kuntze H, Mayer-Steinacker R, Moskopp D, Schneider T, Beringer A, Schlegel U, Stummer W, Welker H, Weyerbrock A, Paulsen F, Rutkowski S, Weller M, Wick W, Kortmann RD, Bogdahn U, Hau P (2018) Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07). Neuro-Oncology 20(3):400–410
18. Padovani L, Sunyach MP, Perol D et al (2007) Common strategy for adult and pediatric medulloblastoma: a multicenter series of 253 adults. Int J Radiat Oncol Biol Phys 68(2):433–440
19. Kann BH, Lester-Coll NH, Park HS et al (2017) Adjuvant chemotherapy and overall survival in adult medulloblastoma. Neuro-Oncology 19(2):259–269
20. Northcott PA, Buchhalter I, Morrissy AS et al (2017) The whole-genome landscape of medulloblastoma subtypes. Nature 547(7663):311–317
21. Liu X, Ding C, Tan W, Zhang A (2020) Medulloblastoma: molecular understanding, treatment evolution, and new developments. Pharmacol Ther 210:107516. https://doi.org/10.1016/j.pharmthera.2020.107516
22. Friedrich C, von Bueren AO, von Hoff K, Kwiecien R, Pietsch T, Warmuth-Metz M, Hau P, Deinlein F, Kuehl J, Kortmann RD, Rutkowski S (2013) Treatment of adult nonmetastatic medulloblastoma patients according to the paediatric HIT 2000 protocol: a prospective observational multicentre study. Eur J Cancer 49: 893–903