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ORIGINAL ARTICLE

Real-world data for pediatric medulloblastoma: can we improve outcomes?

Paula Sedano[1] · Carmen González-San Segundo[1] · Lourdes De Ingunza[1] · Pedro Cuesta-Álvaro[2] · Marta Pérez-Somarriba[3] · Francisco Diaz-Gutiérrez[1] · Carmen Garrido Colino[4] · Alvaro Lassaletta[3]

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Abstract

Medulloblastoma (MB) is a malignant embryonal tumor that develops especially in childhood, with overall survival (OS) at 5 years of up to 70%. The objective of this study is to analyze treatment delivery variables in a retrospective cohort and evaluate the impact of these treatment quality parameters on survival. From 2000 to 2018, 40 pediatric patients with medulloblastoma, treated according to current international protocols, were retrospectively analyzed. Treatment delivery quality indicators were analyzed including the extent of surgery, radiotherapy (RT) parameters, and chemotherapy variables, related with time and dose-intensity deviations. With a median follow-up of 74 months (range, 6–195), OS at 5 years was 74 ± 7%, 81 ± 8% for standard-risk, and 55 ± 16% for high-risk patients ($p = 0.090$). Disease-free survival at 5 years was not significantly affected by extent of surgery ($p = 0.428$) and RT-related variables such as surgery-RT interval ($p = 0.776$) neither RT duration ($p = 0.172$) or maintenance chemotherapy compliance ($p = 0.634$). Multivariate analysis identified risk groups predictive of worse DFS ($p = 0.032$) and leptomeningeal dissemination associated with inferior OS ($p = 0.029$).

Conclusion: Treatment delivery optimization has improved survival rates of patients with MB. Despite this, in our study, we have not established a clear influence of the considered radiotherapy and chemotherapy treatment quality parameters on outcomes.

What is Known:
- *Improvement in treatment modalities during the last decades has reached a 5-year OS of up to 70% in these patients.*
- *Extent of resection and radiotherapy parameters such as interval between surgery-radiotherapy and radiotherapy duration has been described as probable survival prognostic factors.*

What is New:
- *Differences in medulloblastoma survival rates between prospective studies and retrospective series.*
- *The impact on survival of the three main treatment variables, surgery, radiotherapy and chemotherapy, susceptible to improvement.*

Keywords Medulloblastoma · Surgery · Radiotherapy · Survival · Treatment quality · Children

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✉ Alvaro Lassaletta
lassaalvaro@yahoo.com

Paula Sedano
psedanoh@hotmail.com

Carmen González-San Segundo
cglezss@gmail.com

Lourdes De Ingunza
lourdes.ingunza@gmail.com

Pedro Cuesta-Álvaro
pcuesta@ucm.es

Marta Pérez-Somarriba
martaps8@hotmail.com

Francisco Diaz-Gutiérrez
frdiazg@gmail.com

Carmen Garrido Colino
cgarridoc@salud.madrid.org

Extended author information available on the last page of the article

Abbreviations

CG	Children's Oncology Group
ChT	Chemotherapy
CI	Confidence interval
CNS	Central nervous system
CSI	Craniospinal irradiation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
Gy	Gray
HR	Hazard ratio
HTRT	Hyperfractionated radiotherapy
IGRT	Image-guided radiation therapy
MB	Medulloblastoma
MRI	Magnetic resonance imaging
NCDB	National Cancer Database
OR	Odds ratio
OS	Overall survival
PF	Posterior fossa
PNET	Primitive neuroectodermal tumors
RT	Radiotherapy
RTQA	Radiation therapy quality assurance
SE	Standard error
SHH	Sonic hedgehog
SIOP	International Society of Paediatric Oncology
SPSS	Statistical Package for the Social Sciences
STRT	Standard radiotherapy
VMAT	Volumetric modulated arc therapy
WNT	Wingless

Introduction

Medulloblastoma (MB) is the most frequent malignant brain tumor in children and adolescents accounting for 20–25% of all brain tumors. It can occur at any age, with a peak incidence between 4 and 7 years, although recently its incidence has increased in the group of patients aged 10 to 14 years [1, 2]. Around 30% of patients will present with leptomeningeal disease at diagnosis, but it is rare for MB to spread outside the CNS [3]. Medulloblastoma is a very heterogeneous tumor in terms of biology. It is now stratified into different molecular subgroups depending on methylation pattern: Wingless (WNT), Sonic hedgehog (SHH), group 3, and group 4 [4]. Patients are classified into standard or high-risk, according to demographic and tumor factors such as age, leptomeningeal spread, or extent of surgical resection [5, 6]. This classification is essential for the development of a risk-adapted treatment strategy. Improvement in treatment modalities during the last decades has reached a 5-year OS of up to 70% in these patients [2]. However, there is still room for improvement by optimizing treatment quality, especially in low- and medium-income countries. The objective of this study is to analyze treatment delivery variables in a retrospective cohort and evaluate the impact of these treatment quality parameters on survival.

Material and methods

Patient population

This study was approved by the institutional ethics committee. Between 2000 and 2018, 75 children with medulloblastoma received multimodal treatment with curative intent, at two reference hospitals in Spain. Of these, 59 patients were eligible for initial analysis: twelve patients were omitted from this analysis due to lack of complete treatment information and four patients did not receive radiotherapy. Finally, in order to obtain a more homogeneous population, we excluded infants and young children treated with a radiotherapy deferral strategy; therefore, 40 patients were enrolled for the final analysis.

Patient characteristics are shown in Table 1. Mean age was 7.8 years (range, 3–14), with 67.5% being male. All patients had histologic confirmation of medulloblastoma (MB). A craniospinal magnetic resonance imaging (MRI) and cerebrospinal fluid examination to evaluate for disseminated disease were performed at diagnosis. In relation to risk stratification, patients were divided into standard-risk (65%) and high-risk (35%), following the historical risk stratification criteria for medulloblastoma based on clinicopathological variables including age, metastatic stage, and extent of resection. Although since 2012, there is a new classification based in molecular profiling (WNT, SHH, group 3, and group 4); molecular subgrouping was not available for our study [7].

Treatment

All patients underwent surgery, including biopsy alone in 2 patients (5%), subtotal resection (residual tumor by MRI) in 14 patients (35%), and gross total resection in 24 patients (60%). Post-operative MRI was used to determine extent of resection: complete resection (R0), residual disease ≤ 1.5 cm^2 (R1), and residual disease $>$ 1.5 cm^2 (R2). Patients were treated according to different international protocols, with 67.5% of all patients treated as per SIOP PNET 4 (Table 2).

Treatment was largely directed by protocol enrollment and risk group stratification. Patients were treated with surgery followed by radiotherapy (standard or hyperfractionation) and maintenance chemotherapy.

All patients were treated with megavoltage X-rays on a linear accelerator. Patients treated before 2016 were treated

Table 1 Clinical, tumor, and treatment characteristics

Variables	$N = 40$	%
AGE: mean (range) years	7.8 (3–14)	–
Sex:		
Male/female	27/13	67.5/32.5
Histological type:		
Classic MB	29	72.5
Desmoplastic/nodular MB	6	15
Large cell MB	4	10
Anaplastic MB	1	2.5
M stage:		
M0	32	80
M1	2	5
M2	2	5
M3	4	10
Type of surgery:		
Gross total resection	24	60
Subtotal	14	35
Biopsy	2	5
Residual tumor:		
R0	24	60
R1	9	22.5
R2	7	17.5
Risk group:		
Standard-risk	26	65
High-risk	14	35
Protocol:		
SIOP PNET 4	27	67.5
SIOP PNET 5	4	10
ACNS0332	7	17.5
Other	2	5
Dose CSI (Gy):		
≤ 30	27	67.5
> 30	13	32.5
Dose PF:		
≤ 54	23	57.5
> 54	17	42.5
Fractionation:		
Normofractionation	32	80
Hyperfractionation	8	20
Surgery-RT interval (days):		
1–40	29	72.5
> 40	11	27.5
RT duration (days):		
≤ 45	23	57.5
> 45	17	42.5
Concomitant ChT		
Vincristine	24	68.6
Carboplatin	5	14.3
Both	6	17.1
RTChT interval (days)		
≤ 49	33	82.5
> 49	7	17.5
Maintenance ChT compliance		
Optimal dose-intensity	18	45
Optimal number of cycles	37	92.5
Maintenance ChT duration (months)		
≤ 6	14	35
> 6	26	65

MB medulloblastoma, *CSI* craniospinal irradiation, *PF* posterior fossa, *RT* radiotherapy, *Gy* gray, *ChT* chemotherapy

with 3D conformal radiation therapy (29 patients), and patients treated after, with image-guided radiotherapy (IGRT) volumetric modulated arc therapy (VMAT) techniques (11 patients). Computed tomography (CT) scans with contrast were performed for treatment planning, with 2-mm slices for the posterior fossa, and 5-mm slices for the rest of the brain and spinal axis. When feasible, treatment volume delineation was accomplished with image registration of simulation CT scan and the initial diagnostic MRI. Volume delineation was as per standard of care or per enrolled protocol. The organs at risk were the healthy brain, lens, globes, optic nerves, chiasm, pituitary, cochlea, hippocampus, parotid glands, spinal cord, lungs, thyroid, heart, liver, kidneys, bladder, rectum, testicles, and ovaries. Fourteen (35%) children required sedation during radiotherapy, with a mean age of 6.2 years (range, 3–14 years).

Craniospinal doses ranged from 23.4 to 39.8 Gy (mean, 27.5 Gy). More than half of the patients ($n = 27$) received reduced dose craniospinal radiation with 23.4 Gy [8, 9]. Posterior fossa doses ranged from 54 to 61.2 Gy (mean, 55.6 Gy), with a boost to the tumor bed or residual tumor of up to 68 Gy in 7 patients (17.5%). In the majority of protocols, radiotherapy doses were delivered once a day using 1.8 Gy per fraction, with the exception of patients included in HIT-SIOP PNET 4, who were treated twice a day with doses of 1.0 Gy per fraction.

Radiotherapy initiation within 40 days after surgery was considered optimal. For ideal treatment compliance, patients had to receive radiotherapy continuously (daily, except weekends and holidays), completing treatment in 45 days or less. According to protocol, some patients received weekly and/or daily chemotherapy during radiotherapy treatment. Maintenance chemotherapy had to start within 6 to 7 weeks after end of radiotherapy for correct timely delivery. For ideal chemotherapy compliance, patients had to receive all cycles, 6 to 8 courses depending on the protocol, within the established timeframe and without dose reduction or drug modification.

In a first analysis, these maintenance chemotherapy parameters were studied separately: agents or dose modifications within each cycle, treatment delays, and total number of courses received. In a second time, we studied the overall maintenance chemotherapy compliance by creating a variable covering all these aspects.

Statistical analysis and outcomes

A statistical analysis was performed using the SPSS 21.0 [10]. Disease-free survival (DFS) and overall survival (OS) was evaluated by Kaplan-Meier non-parametric statistical analysis. Disease-free survival was defined as the time from first diagnosis to first relapse, progression, or last follow-up date. Overall survival was determined as the time from diagnosis to death from any cause or last follow-up. p values less than 0.05 were considered statistically significant. A multivariate analysis was performed although the results were limited due to the small sample size.

Results

With a median follow-up of 74 months (range, 6–195), the 5-year OS of all 40 patients was of 74 ± 7%. When analyzing survival by risk group, 5-year OS was 81 ± 8% for standard-risk and 55 ± 16% for high-risk ($p = 0.090$) (Fig. 1a/b). Disease-free survival at 5 years was 66 ± 8%, 77 ± 8% for standard-risk, and 40 ± 15% for high-risk ($p = 0.024$) (Fig. 1c/d). Extent of resection had an effect on 5-year DFS, with patients with R0/R1 having superior outcomes compared with R2, although this was not statistically significant (69 ± 8 versus 48 ± 23%, respectively; $p = 0.428$).

Regarding radiotherapy, 29 patients (72.5%) started treatment within 40 days of surgery as per protocol with a median interval time of 34 days (range 2–40 days). Radiotherapy treatment delay was mainly due to the following: technical aspects of the linear accelerator ($n = 6$), post-operative toxicity ($n = 3$), mostly neurological complications, or unknown for 2 patients. With respect to treatment duration, 57.5% patients ($n = 23$) received optimal radiotherapy (≤ 45 days). Interruptions were mainly caused by RT and/or concurrent chemotherapy toxicity ($n = 3$), extended holidays ($n = 2$), technical linear accelerator problems ($n = 3$), disease sequelae ($n = 1$), or unknown cause ($n = 8$).

As for chemotherapy, 35 patients (87.5%) were treated with concomitant chemotherapy during radiotherapy, with vincristine ($n = 24$), carboplatin ($n = 5$), or both (n = 6), having five of these patients dose modification due to toxicity. The majority of patients ($n = 33$) initiated maintenance chemotherapy within 7 weeks after the end of radiotherapy. Regarding maintenance chemotherapy compliance, up to 55% presented agents or dose-intensity deviations, predominantly involving platinum-based drugs ($n = 8$) or several drugs ($n = 8$). Despite this, the majority of patients, 92.5%, received all planned number of cycles. When analyzing total compliance, less than half of the patients ($n = 17$) received maintenance chemotherapy regimen conforming to protocol (all cycles with no interruptions or drug/dose modifications).

When evaluating the impact of radiotherapy parameters on outcomes, DFS at 5 years was 64 ± 9% for patients starting radiotherapy within 40 days of surgery, and 70 ± 15% for patients with treatment delay ($p = 0.776$). Regarding treatment duration, DFS at 5 years was 59 ± 11% for treatment within 45 days and 75 ± 11% for prolonged treatment ($p = 0.172$).

Receiving concomitant chemotherapy during radiotherapy did not alter DFS at 5 years (67 ± 8% for patients with concomitant treatment versus 60 ± 22% for patients without it; $p = 0.780$), although there was a trend towards better 5-year OS for patients with chemotherapy during irradiation (76 ± 8% with concomitant chemotherapy versus 60 ± 22% without it; $p = 0.560$). The interval between the end of irradiation and the beginning of maintenance chemotherapy, with the established 49 days cut-off point, did not have an impact on DFS (< 49 days 61 ± 9% versus > 49 days interval 86 ± 13%; $p = 0.444$) neither on OS (< 49 days 71 ± 8% versus >49 days interval 86 ± 13%; $p = 0.705$). However, when setting the cut-

Table 2 Current protocols treatment regimen

Protocol	Multimodal treatment	Radiotherapy doses	Concomitant chemo	Chemotherapy
SIOP PNET 4 Standard-risk	Surgery + RTChT + ChT	STRT: - CSI 23.4 Gy - PF 54 Gy HFRT: - CSI 36 Gy - PF 60 Gy - Tumor bed 68 Gy	Vincristine	Maintenance Vincristine, cisplatin, lomustine
SIOP PNET 5 Standard-risk/Low-risk *No low-risk patients included in our study	Surgery + RTChT + ChT	Standard-risk:CSI 23.4 Gy PF 54 Gy	With or without concomitant carboplatin	Maintenance Cycle A: vincristine, cisplatin, lomustine Cycle B: vincristine, cyclophosphamide *Alternating cycles
ACNS0332 High-risk	Surgery + RTChT + ChT	CSI 36 Gy PF 55.8 Gy	Vincristine alone or vincristine and carboplatin	Maintenance Vincristine, cisplatin, cyclophosphamide

RT, radiotherapy; *ChT*, chemotherapy; *STRT*, standard treatment radiotherapy; *HFRT*, hyperfractionated radiotherapy; *CSI*, craniospinal irradiation; *PF*, posterior fossa; *Gy*, gray

off interval in 41 days, patients with early maintenance chemotherapy initiation ($n = 16$) showed a statistical significant detriment in DFS (≤ 41 days 36 ± 15% versus > 41 days interval 78 ± 8%; $p = 0.008$) and in OS (≤ 41 days 42 ± 16% versus > 41 days interval 86 ± 7%; $p = 0.010$).

When analyzing maintenance chemotherapy compliance, patients who had a drug or dose-intensity modification presented greater 5-year DFS compared with those who received full dose with no drug modification although this was not statistically significant ($p = 0.816$). However, the number of cycles delivered had an impact on survival rates, with a 5-year OS of 77 ± 7% for patients receiving all cycles versus 33 ± 27% for patients not completing all cycles ($p = 0.013$). When studying overall maintenance chemotherapy compliance, patients with optimal compliance did not have better 5-year OS compared with those with any treatment delivery deviation (75 ± 11% for optimal compliance versus 73 ± 10% for patients with modifications during treatment delivery; $p = 0.948$).

On both univariate (Table 3) and multivariate analysis (Table 4), neither extent of surgery, radiotherapy parameters, nor chemotherapy compliance was found to alter significantly OS and DFS. Multivariate analysis identified leptomeningeal dissemination (0.029) and high-risk group (0.032) as negative prognostic factors (Table 4).

When analyzing survival rates for all 59 patients, the 5-year OS was 58 ± 7%, 80 ± 8% in standard-risk group, and 39 ± 10% in high-risk group ($p = 0.009$). Disease-free survival at 5 years was 51 ± 7%, 73 ± 9% for standard-risk, and 34 ± 9% for high-risk ($p = 0.008$). On both univariate and multivariate analysis, neither radiotherapy timing nor radiotherapy duration were found to alter significantly OS and DFS. The multivariate analysis identified leptomeningeal dissemination ($p = 0.049$) and residual disease R2 ($p = 0.016$) as predictors of worse disease-free survival.

Discussion

Medulloblastoma is treated with multimodal treatment combining surgery, radiotherapy, and chemotherapy. During the past decades, improvements in these treatment modalities have increased long-term survival to a 5-year OS of 60–70% [11, 12]. A 39% reduction in mortality rate was obtained for patients diagnosed from 2000 onwards versus those diagnosed between 1990 and 1999 in a retrospective study from England that included patients diagnosed with medulloblastoma [13].

In our study, survival rates are in line with those present in other European countries and slightly inferior to prospective trial survival outcomes [8, 14–16]. When analyzing survival in patients with high-risk MB, our results are in line with the

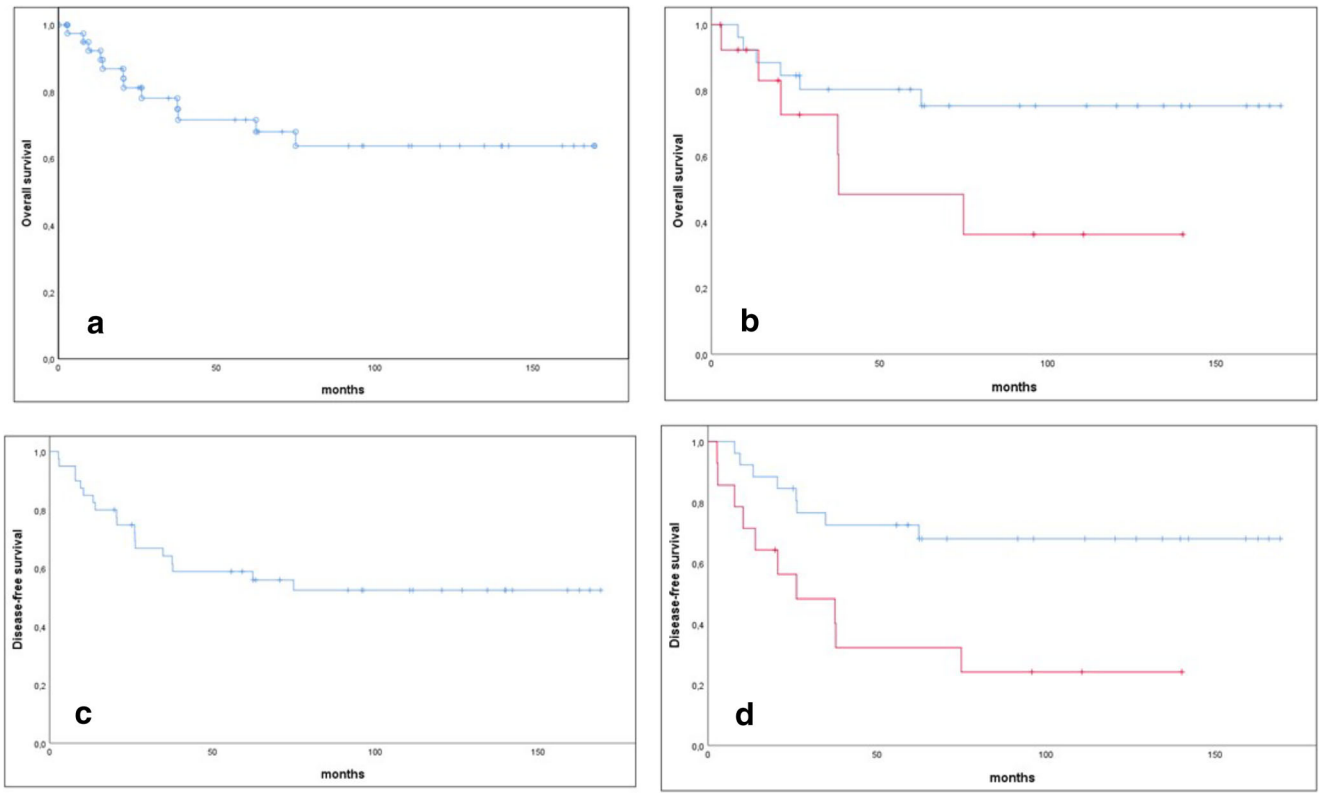

Fig. 1 Kaplan-Meier survival rates. a OS, overall survival for all patients ($n = 40$). **b** Overall survival by risk group. **c** DFS, disease-free survival for all patients. **d** DFS, disease-free survival by risk group. Standard-risk (blue) and high-risk patients (red)

Table 3 Univariate analysis - log rank (Mantel-Cox)

Treatment variables	5-year (OS)	*p*	5-year (DFS)	*p*
Residual disease ≤ 1.5 cm^2	76 ± 8%	$p = 0.746$	69 ± 8%	$p = 0.428$
Residual disease > 1.5 cm^2	56 ± 25%		48 ± 23%	
RT PF dose ≤ 54 Gy	78 ± 9%	$p = 0.402$	74 ± 9%	$p = 0.215$
RT PF dose > 54 Gy	65 ± 13%		53 ± 13%	
RT CSI dose ≤ 30 Gy	78 ± 8%	$p = 0.608$	74 ± 9%	$p = 0.227$
RT CSI dose > 30 Gy	60 ± 16%		44 ± 16%	
Surgery-RT interval ≤ 40 days	75 ± 8%	$p = 0.819$	64 ± 9%	$p = 0.776$
Surgery-RT interval > 40 days	70 ± 15%		70 ± 15%	
RT duration ≤ 45 days	72 ± 10%	$p = 0.443$	59 ± 11%	$p = 0.172$
RT duration > 45 days	75 ± 11%		75 ± 11%	
Received ChT during RT	76 ± 8%	$p = 0.560$	67 ± 8%	$p = 0.780$
No ChT during RT	60 ± 22%		60 ± 22%	
RT-mChT interval < 49 days	71 ± 8	$p = 0.705$	61 ± 9%	$p = 0.444$
RT-mChT interval > 49 days	86 ± 13		86 ± 13%	
mChT received full dose/drug	76 ± 10%	$p = 0.889$	65 ± 12%	$p = 0.816$
mChT dose/drug modification	71 ± 10%		66 ± 11	
mChT completed full number of cycles	77 ± 7%	$p = 0.013$	68 ± 8%	$p = 0.040$
mChT number of cycles reduction	33 ± 27%		33 ± 27%	
mChT optimal compliance	75 ± 11	$p = 0.948$	63 ± 12%	$p = 0.634$
mChT suboptimal compliance	73 ± 10		68 ± 10%	

OS, overall survival; *DFS*, disease-free survival; *CSI*, craniospinal irradiation; *PF*, posterior fossa; *RT*, radiotherapy; *Gy*, gray; *mChT*, maintenance chemotherapy

ones described in previous studies, including those with deferred radiotherapy treatment strategy, with 5-year OS rates ranging between 40 and 75% [17–22]. In our study, 6 patients (15%) were classified as high-risk MB because of M2–M3 involvement, with a 5-year DFS of 21%. In this subgroup with disease dissemination, the 10-year DFS rate reported by Van Hoff et al. [17] was 32%. Prior phase III studies analyzing patients with high-risk MB published survival rates above 70%, rates that have not been reproduced in retrospective series [17–19]. The rigorous selection of patients from prospective clinical trials, the required start time of radiation within 28 days after surgery (COG trials), the proportion of enrolled M1–M3 patients, and the size of the residual tumor are factors that can explain these differences in survival between prospective and retrospective studies [6, 23–25].

More agreement is found when analyzing the impact of post-surgical residual tumor in survival. Lannering et al. published in a prospective randomized trial that a post-operative residual tumor > 1.5 cm^2 based on post-operative CT scan had a profound, detrimental impact on survival ($p < 0.01$) [12]. A population-based study from the Oslo University Hospital, which included 175 patients with MB or CNS PNET, also found an improvement in 5-year OS in patients with gross total resection versus subtotal resection (64 versus 22%, respectively) [26]. Nonetheless, Thompson et al., in the molecular era, published a retrospective study, assessing the effect of surgery extent on survival within the different molecular subgroups (WNT, SHH, group 3, and group 4) [27]. Extent of resection was classified into three categories based on the post-operative imaging (MRI for most cases): "gross total resection" (no residual tumor), "near-total resection" (< 1.5 cm^2

Table 4 Multivariate analysis

n = 40 patients						
Variable	B	SE	Sig	Hazard ratio	95% CI lower	95% CI upper
Risk group	1.122	0.524	0.032	3.071	1.101	8.572
High versus standard						
M stage	1.367	0.625	0.029	3.924	1.152	13.364
M2M3 versus M0M1						

B, beta coefficient; *SE*, standard error; *R2*, residual tumor > 1.5 cm^2; *R0R1*, residual tumor ≤ 1.5 cm^2; *CI*, confidence interval

of residual disease), and "sub-total resection" (1.5 cm^2 or above). Significant survival benefit was observed for gross total resection over subtotal resection. Interestingly, in a molecular subgroup sub analysis, maximum resection provided benefit in progression-free survival only for patients with group 4 medulloblastoma (total versus subtotal resection; HR 1.97, 1.22–3.17, $p = 0.006$). In our study, although there is a numerical detriment in survival for those patients undergoing suboptimal surgery, this was not statistically significant, which could be in relation to the small sample size.

Regarding the influence of radiotherapy parameters, the interval between surgery and radiotherapy, as well as duration of radiotherapy, has been described as probable survival prognostic factors. One of the first studies to observe a relation between radiotherapy duration and outcome was a 30-year review, which included 53 patients treated with radiotherapy with curative intent at the University of Florida [28]. Five-year posterior fossa control was 89% for those treated within 45 days versus 68% for prolonged duration ($p = 0.010$). Multivariate analysis for local control identified radiotherapy duration as the only statistically significant prognostic factor ($p = 0.030$). Taylor et al. reported the impact of radiotherapy parameters on outcome, including radiotherapy duration, surgery-radiotherapy interval, dose, and targeting deviations [29]. Three-year OS and DFS were better for those who completed treatment within 50 days as established in PNET-3 protocol recommendations (OS 84 versus 71%, $p = 0.036$ and DFS 79 versus 54%, $p = 0.009$). The main cause of delay was treatment toxicity (mainly myelosuppression in the chemotherapy group) followed by technical problems related to the facility or holidays; similar to our results. Multivariate analysis revealed use of chemotherapy ($p = 0.025$) and radiotherapy duration ($p = 0.010$) as the only parameters predictive of better DFS. Kann et al. retrospectively analyzed radiotherapy timing in young children (3 to 8 years old) [30]. Patients were divided into two groups, those receiving upfront post-operative radiotherapy (treatment within 90 days of surgery) and those having delayed post-operative radiotherapy. Although radiotherapy deferral has gained acceptance in children under 3 years old, for patients in this study, delayed radiotherapy was associated with poorer OS in multivariable analysis (HR 1.95; 95% CI, 1.04–2.94).

Contrary to the aforementioned, results from a series published by Frost et al. proved no relation between disease-free survival and radiotherapy variables (doses or radiotherapy treatment duration) [31]. However, it is important to recall that patients in this study were over 16 years old and were treated in some cases with different radiotherapy techniques (Cobalt-60) and doses. Back et al. analyzed treatment prognostic factors such as radiotherapy duration for patients treated from 1980 to 1993 [32]. On this retrospective study, median radiotherapy dose to the posterior fossa, radiotherapy timing and radiotherapy duration were 55 Gy, 42 days, and 45 days, respectively. On multivariate analysis, the only treatment prognostic factor strongly associated with local control was radiotherapy dose to posterior fossa ($p = 0.004$). However, in this analysis, extended radiotherapy duration, especially above 46 days, was nearly associated with poorer disease control (OR of 1.02 [95% CI 0.96–1.08]; $p = 0.049$). In our series, survival in relation to radiation doses was analyzed but was difficult to interpret as delivered doses depended mainly on protocol inclusion, which in turn depended on risk group; therefore, high-risk patients generally received higher craniospinal and posterior fossa doses than standard-risk patients.

On a recent analysis of the National Cancer Database (NCDB), data from 1338 patients with medulloblastoma treated with curative intent, multimodal therapy was collected [33]. The ideal interval between surgery and the start of radiation was set on 3.1–4 weeks. It was shown that patients starting radiotherapy within 3 weeks from surgery had a decreased 5-year OS compared with those treated within the stipulated timing both in the univariate ($p = 0.003$) and multivariate analysis ($p = 0.004$). These results could be related to the fact that patients with early radiotherapy initiation tended to be those with worse prognostic factors (younger patients, M1–M3 disease, or/and subtotal resection). However, in the remaining patients, a delay on radiotherapy treatment (> 5 weeks) did not have a significant impact on survival, as long as the interval did not exceed 90 days ($p = 0.563$). Therefore, radiotherapy timing should allow adequate post-surgery recovery instead of focusing on meeting the 4 to 6 weeks window required by the majority of trials.

To summarize, the impact on survival of radiotherapy treatment variables remains a controversial issue, although there is a general agreement on beginning radiotherapy within 4 to 6 weeks from surgery and minimizing delays during radiotherapy. In fact, the National Cancer Institute for pediatric tumors includes, as priority matter, radiation issues such as treatment delay or omission [34].

In a recent study, Rojas et al. defined, as quality indicators for radiotherapy treatment, the percentage of patients initiating radiotherapy within 40 days after surgery (68%) but they did not analyze if this had an impact on survival [35]. For maintenance chemotherapy treatment delivery, they considered the number of patients with dose-intensity modification (26%) or time-intensity modifications (42%) as negative quality indicators. However, we did not find in the reviewed literature any reference regarding the prognostic influence of chemotherapy compliance. According to SIOP PNET 4 and 5 protocols, patients should start maintenance chemotherapy 6 weeks after the end of radiation treatment, and administered doses of both concomitant and maintenance chemotherapy should be tested for prognostic relevance [36, 37]. In the present study, optimal chemotherapy compliance was not associated with better outcomes. Although delay in chemotherapy starting date after

radiotherapy did not resulted in worse outcomes, early initiation (< 6 weeks after end of radiotherapy) was associated significantly with a survival detriment. This could be related to the fact that patients who initiated maintenance chemotherapy before the established 6 weeks period tended to have more advanced disease at diagnosis or worse response to initial treatment.

The main objective of this study was to establish treatment delivery quality in medulloblastoma patients and further analyze their prognostic impact. Nonetheless, the limitations of our study need to be acknowledged, starting with the issues inherent in any retrospective analysis, in a period of 15 years, during which time different treatment protocols have emerged. Furthermore, in relation to patient classification, patients treated in the first decade (2000–2010) could have been misclassified as no molecular biological analysis was performed in them. Due to the small sample size, most of the results obtained regarding treatment quality parameters did not reach statistical significance.

The strengths of the study relate to the inclusion of patients treated in the same radiation oncology center, with international protocols and all with megavoltage techniques and CT treatment simulation. We analyzed the three main treatment variables, susceptible to improvement, and their impact on survival. Hopefully, the improvement of these treatment variables (complete resection, early initiation of radiotherapy after surgery, optimal treatment duration, and total chemotherapy compliance) along with the systematic application of quality control programs such as RTQA (radiation therapy quality assurance) will optimize survival rates and bring them closer to those achieved in prospective clinical trials [38].

In absence of studies that can confirm the influence of radiotherapy timing and chemotherapy compliance on survival for patients with medulloblastoma, our study has not found a prognostic association. Subtotal resection is the only treatment parameter associated with worse survival outcomes, although in the present study this finding did not reach statistical significance. Although higher survival rates have been published by prospective studies that recommend early radiotherapy initiation (preferably within 28 days), and duration within 45–50 days, its prognostic impact has not been proven in the majority of institutional series. The current evolution of radiotherapy techniques, allowing greater precision, together with mandatory daily image-guided quality control and the emphases on radiotherapy timing compliance are elements that can be easily improved in order to potentially optimize survival outcomes.

Up to now, complete resection without neurological sequelae, optimal chemotherapy, and radiation treatment, along with the fundamental quality control in the delivery of these treatments, are the mainstays to achieve the survival rates obtained in reference centers. In the near future, individualized treatment strategies based on molecular subgroups, the introduction of new drugs and the real possibility of irradiating all patients with proton therapy within the appropriate time, will help improve the survival of children with medulloblastoma.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Paula Sedano, Carmen González-San Segundo, Lourdes De Ingunza, Pedro Cuesta-Alvaro, and Alvaro Lassaletta. The first draft of the manuscript was written by Paula Sedano, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Ethics approval Ethical approval was waived by the local Ethics Committee of Hospital Universitario Niño Jesus linked to University Autonoma de Madrid. In view of the retrospective nature of the study, all the procedures being performed were part of the routine clinical care.

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

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Affiliations

Paula Sedano[1] · Carmen González-San Segundo[1] · Lourdes De Ingunza[1] · Pedro Cuesta-Álvaro[2] · Marta Pérez-Somarriba[3] · Francisco Diaz-Gutiérrez[1] · Carmen Garrido Colino[4] · Alvaro Lassaletta[3]

[1] Radiation Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[2] Computing Services, Research Support, Complutense University of Madrid, Madrid, Spain

[3] Department of Pediatric Oncology, Hospital Infantil Universitario Niño Jesús, Avenida Menéndez Pelayo, 65, 28009 Madrid, Spain

[4] Pediatric Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain