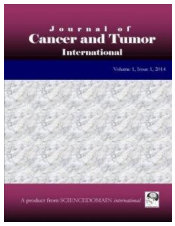

Journal of Cancer and Tumor International
5(3): 1-11, 2017; Article no.JCTI.33525
ISSN: 2454-7360

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Outcome and Predictive Factors of Radiation Therapy for Medulloblastoma: Mansoura Experience

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Authors' contributions

This work was carried out in collaboration between all authors. Author DAEG wrote the protocol, performed the statistical analysis and the first draft of the study. Author MFA designed the study and managed the literature searches. Author AH revised the statistical analysis and the first draft. Author ME revised the whole work. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JCTI/2017/33525
Editor(s):
(1) William C. S. Cho, Queen Elizabeth Hospital, Hong Kong.
Reviewers:
(1) Wenyin Shi, Thomas Jefferson University, USA.
(2) Ronald Bartzatt, University of Nebraska, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history/18879

Original Research Article

Received 19th April 2017
Accepted 27th April 2017
Published 2nd May 2017

ABSTRACT

Background: Medulloblastomas are the most common infratentorial malignant brain tumors with an incidence rate of 0.5 in 100.000 typically arising in childhood at age 5-9 years.
Aim of Work: Exploring the epidemiological characteristics, treatment outcome and prognostic factors of medulloblastoma patients whom were referred to Mansoura Clinical Oncology &Nuclear Medicine Department for adjuvant treatment through the period from Jan. 1997 to Dec. 2011 inclusive.
Patients and Methods: Sixty-Two patients records were in harmony with the eligibility criteria . Males were slightly larger in number [33 cases (53%)]. The majority of the cases were of pediatric age (42 patient representing 68%). Complete resection was possible in only 31 cases (50%).The classic type was the commonest [36 cases (58%)]. The majority were of the of M0 stage [52 cases (84%)] and of high risk category [37 cases (60%)]. Median dose to posterior fossa was 52.5 Gray (range, 43-56 Gray). The Chemotherapy was administrated in forty-seven patients (75.8%). The toxicity of treatment were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).
Results: Adjuvant Radiotherapy was generally well tolerated. The median overall survival time and median progression – free survival were 90 & 72 months respectively. Relapse was reported in 28

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patients (45.16%).M staging, extensiveness of resection, hydrocephalus at presentation and time elapsed till radiotherapy all affected significantly the prognosis.
Conclusion: In conclusion, this study highlights the effect of stage, completeness of surgery, and early initiation of adjuvant radiotherapy on the outcome.

Keywords: Medulloblastoma; craniospinal radiotherapy; posterior fossa tumors; concomitant chemoradiotherapy; matching of multiple radiotherapy fields; radiotherapy toxicity.

1. INTRODUCTION

Medulloblastomas are the most common infratentorial malignant brain tumors with an incidence rate of 0.5 in 100.000 typically arising in childhood at age 5-9 years. They are thought to originate from the neuroepithelial lining of the upper fourth ventricle [1]. It seems that a multimodality approach is the cornerstone of treatment [2]. The standard detailed radiation regimen comprised of radiation to the entire craniospinal axis followed by a boost to the whole posterior fossa, for a total dose of 54 Gray [3]. Cisplatinum-based chemotherapy is usually added to the therapy regimen for medulloblastoma [4]. The use of post irradiation chemotherapy to allow radiation dose reduction is becoming increasingly common especially for children but optimal use of adjuvant chemotherapy is still unclear for adult patients [2]. The prognosis of medulloblastoma is related to several clinical and pathological criteria such as: Modified Change staging, age, completeness of resection, histological subtype and genetic markers [5].

1.1 Aim of Work

The aim is to explore the epidemiological characteristics, treatment outcome and prognostic factors from the records of medulloblastoma patients whom were referred to Mansoura Clinical Oncology & Nuclear Medicine Department for adjuvant treatment through the period from Jan. 1997 to Dec. 2011 inclusive.

2. PATIENTS AND METHODS

This retrospective study was performed in accordance with the institutional ethical policies. Between Jan 1997 and Dec 2011 inclusive, one hundred and twenty-three patients with histologically confirmed MB were recorded in Clinical Oncology & Nuclear Medicine Department, Mansoura University Hospital. However, only 62 patients records were included in this study according to the eligibility criteria.

2.1 Eligibility Criteria

1. Fully staged, pathologically proven MB cases who underwent initial neurosurgical tumor resection followed by postoperative radiation in the form of CSI with boost to the posterior fossa area.
2. No other primary tumors.
3. No major co morbidity.
4. The patients complied to regular follow up at least for some time post treatment.

Various aspects were analyzed in the records such as epidemiology, detailed history, presentation, physical and neurological examinations, Karnofsky Performance Scale (KPS), and brain magnetic resonance (MR) images. Moreover, the treatment plan ,treatment outcome, survival and disease status at follow-up visits were recorded. Emphasis was given on prognostic factors and their effect on treatment outcome.

2.2 Patient Characteristics

Tables (1a and 1b) presented the patient characteristics. Males were slightly larger in number [33 cases (53%)]. The majority of the cases were of pediatric age (42 patient representing 68%). Vomiting either alone or with other symptoms was the commonest presentation [50 cases (81%)].

2.3 Pre-surgical Workup

Complete laboratory profile was done. Complete staging of the craniospinal axis was performed using MR-imaging as well as examination of the cerebrospinal fluid (CSF).

2.4 Surgery

All patients underwent neurosurgical resection before RT. Resections were performed to the extent compatible with good neurological

outcome. Extent of resection was defined on the basis of surgical reports, pathological reports, and postoperative imaging. Table 2 showed surgeries done. Complete resection was possible in only [31 cases (50%)], while ventriculo – peritoneal (VP) shunt was required in [18 cases (29%)] of the cases.

Table 1a. Demographic patients' characteristics

Parameter		N=62	
		Number	Percentage
Sex	Male	33	53.2%
	Female	29	46.8%
Age	>18	20	32.3%
	>3-18	41	66.1%
	</=3	1	1.6%

Table 1b. Patients initial symptoms

Parameter	Number N=62	Percentage (%)
Vomiting	50	81
Headache	44	71
Cerebellar symptoms	40	65
Cranial nerve affection	27	44

Pathological diagnosis was determined in all patients according to the World Health Organization (WHO) Classification [6]. The classic type was the commonest [36 cases (58%)]. The majority of the tumors were midline in location [44 cases (71%)], of M0 stage [52 cases (84%)] according to the Chang system [7]) and of high risk category [37 cases (60%)] according to the risk stratification system of medulloblastoma [8] (Table 3).

Table 2. Characteristics of surgery

Extent of surgery	Complete excision	31	50%
	Partial excision	25	40.3%
	Just biopsy	6	9.7%
VP shunt*	VP shunt	18	29%
	No VP shunt	44	71%

*VPshunt *: ventriculo-peritoneal shunt*

All patients underwent postoperative irradiation in the form of cranio- spinal radiotherapy (CSRT) with a boost to the posterior fossa. The median duration from the surgical interference till the start of post-operative radiotherapy was 2 months. In our department till the end of 2011, all patients were treated by conventional 2D radiotherapy. The patients were treated in the prone position with an individual facial support and a shell down over the neck to immobilize the head and neck. The initial volume included the whole brain and extended to the inferior border of the third or fourth cervical vertebra. It included also the spine which was treated from the fourth or fifth cervical vertebra to the fourth sacral foramina to include the theca and sacral nerve root. After that, a boost to the posterior cranial fossa was given to increase the dose to the

Table 3. Tumor characteristics

Parameter	Number N=62		Percentage
Pathology	Classic MB	36	58.1%
	Desmoplastic MB	24	38.7%
	Large cell MB	1	1.6%
	Anaplastic MB	1	1.6%
Tumor position	Midline	44	71%
	Lateralized	18	29%
M Stage	M0	52	83.9%
	M1	7	11.3%
	M2	0	0.0%
	M3	3	4.8%
T stage	T1	5	8%
	T2	24	39%
	T3	22	35%
	T4	11	18%
Risk category	Standard	25	40%
	High	37	60%

primary tumor site. The whole brain and the boost were treated isocentrically using opposing lateral beams, while the spine was treated by two direct adjacent fields to cover the whole spinal cord (One field was used in preschool ages). Gap calculation was done to find the required space between the fields [9]. Fig. 1 illustrates gap calculation.

Median CSRT dose was 35 Gy (range, 23.4-36 Gy), and median dose to posterior fossa was 52.5 Gy (range, 43-56 Gy); median dose per fraction was 1.8 Gy. Two cases received suboptimal total dose,one received 43 Gy and the other 49 Gy. The first case stopped the sittings due to typhoid fever while the other one stopped due to family problems and both resumed the follow up after 8 and 10 weeks respectively. Radiation was delivered with linear accelerators, 6-MV photon energies, according to the standard protocols. Steroids (dexamethasone intravenously in three divided doses plus H2 receptor blocking drugs) were given.

2.4.1 Chemotherapy

Chemotherapy was administrated in forty-seven patients (75.8%). Twenty-eight patients (45.2%) received chemotherapy as adjuvant treatment, seven patients (11.3%) received chemotherapy after relapse and 12 patients (19.4%) received chemotherapy both as adjuvant treatment and after relapse. The 47 patients who received chemotherapy were 36 pediatric patients (<18 years), and only 11 adult patients. Combined chemo-radiotherapy with weekly injections of vincristine was given to only 8 patients (12.9%), as most of the patients in this study were treated before adoption of such CCRT protocol in our department. The regimens of chemotherapy used, either as adjuvant or after relapse, were shown in Table 4.

2.4.2 Follow up

Imaging studies were done 4-8 weeks post treatment and were repeated every 3 months in the first year and every 6 months in the second year. In the subsequent years the rate of imaging gradually slowed down.

2.4.3 Toxicity

The toxic effects of the treatment were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

2.4.4 Statistical analysis

Quantitative data were summarized as medians and (minimum-maximum values), while qualitative data as percentages. Comparisons of group medians were done using the Mannwhitney U test and kruskal-Wallis test, while comparisons of percentages were done by Chi-square test. Overall survival (OS) was calculated from the date of primary diagnosis until the date of last follow-up or death. Progression-free survival (PFS) was calculated in months from the date of initial diagnosis until the first imaging modality showing recurrent disease. Survival of patients was displayed as Kaplan-Meier survival curve. Multivariate analysis was performed using a Cox regression analysis. Multivariate analysis was done on the survival predictors that showed significance in the univariate analyses. The results have been considered significant if p value is ≤0.05.All statistical analyses were performed using a software tool (SPSS 15.0).

Table 4. Regimens of chemotherapy

Type of chemotherapy used	N=47	Percentage
	Number of patients	
PCV protocol*	14	22.5%
Carboplatin-vepsid	7	11.2%
Carboplatin-vincristine	3	4.8%
ICE protocol**	3	4.8%
Vincristine, vepside, carboplatin alternating with vincristine, vepsid and cyclophosphamide	2	3.2%
Cisplatin-vepsid	1	1.6%
CCNU, carboplatin, vincristine	1	1.6%
Intrathecal methotrexate	1	1.6%
Vincristine, methotrexate	1	1.6%
Unknown regimen	13	20.9%

** PCV protocol: Procarbazine, CCNU, Vincristine, **ICE protocol: Ifosfamide, Carboplatin, Etoposide*

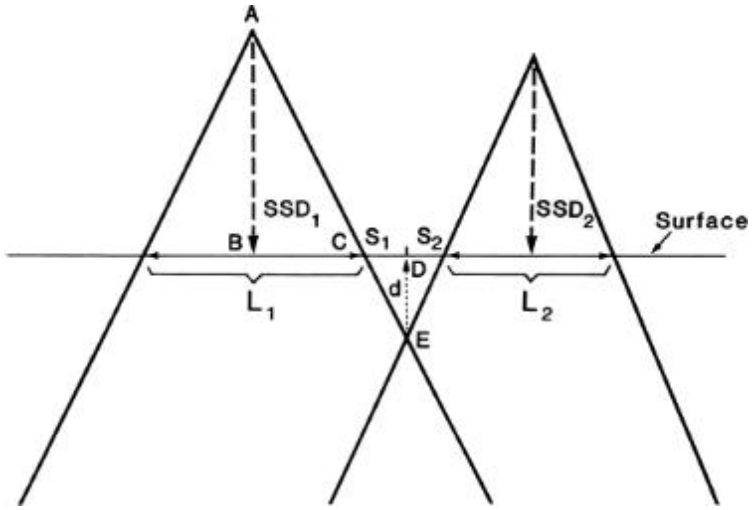

Fig. 1. Geometry of two adjacent fields

S=S1+S2, S1=$1/2L1\left(\frac{D1}{SSD1}\right)$*, S2=*$1/2L2\left(\frac{D2}{SSD2}\right)$*, L1,L2 =Length of field size*
D1, D2=Depth of each field, S=Gap length

3. RESULTS

The median follow up time was 90 months (range 4-176).

3.1 Toxicity

Adjuvant RT was generally well tolerated. Acute radiation toxicity was relatively mild. Most patients suffered mild malaise, and neusea. Acute sever toxicity was reported in patients who received chemotherapy. Among 47 patients who received chemotherapy, 9 cases(20%) developed grade III neutropenia, 3 patients (6%) developed grade III mucositis. Lastly grade III dermatitis was observed in also 3 patients (6%).Chronic toxicity in the form of peripheral neuropathy , developed in 4/47 (8.5%) patients, all of whom had been treated with vincristine. One patient, who had received cisplatin developed ototoxicity. Mental development was impaired in 3 /47 patients (6%).

The median OS time was 90 months (range 4-176), while the median PFS was 72 months (range 4-150months), Figs. (2 and 3 respectively). The median PFS was 29 months (range 7-150 months) in cases relapsing in the posterior fossa, while it was 33.5 months (range 4-64 months) for other non- distant relapses. The only case with distant metastasis occurred after 35 months. Relapse was reported in 28 patients (45.16%). The relapse was either in the posterior fossa only, the rest of the brain, the spinal cord or distant. Patterns of relapse were shown in Table 5.

Table 5. Relapse

Parameter			Number N=62	Percentage
Relapse	No relapse		34	54.8%
	Relapse		28	45.16%
		Isolated posterior fossa relapse	13	32.3%
		Posterior fossa relapse +spinal relapse	6	9.6%
		Isolated spinal relapse	3	4.8%
		Isolated brain relapse	4	6.4%
		Spinal and brain relapse	1	1.6%
		Lung relapse+posterior fossa relapse	1	1.6%

The 28 relapsed cases , were managed as followed:15received chemotherapy,6 received chemoradiotherapy,4underwent surgery,1 received stereotactic radiotherapy,1 underwent surgery plus receiving chemotherapy and 1 underwent surgery plus receiving chemo radiotherapy.

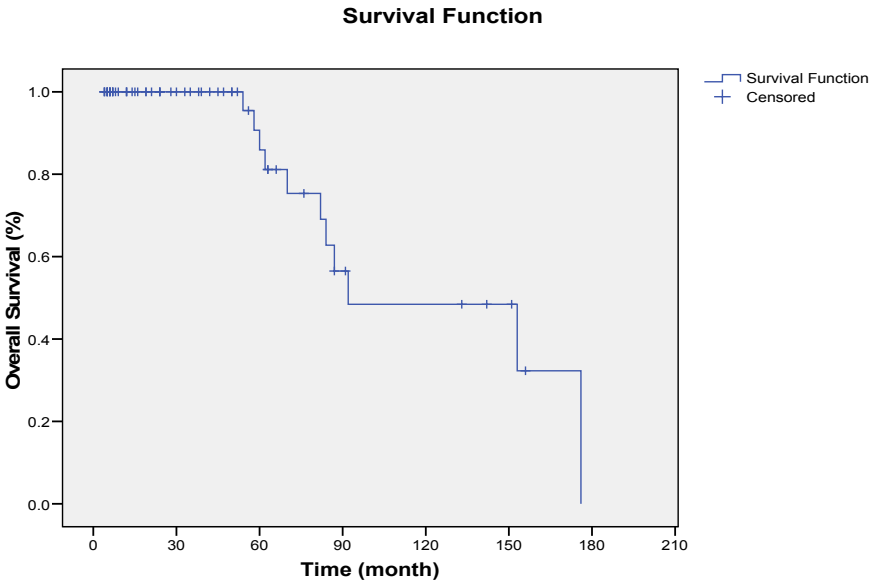

Fig. 2. OS of all the studied population

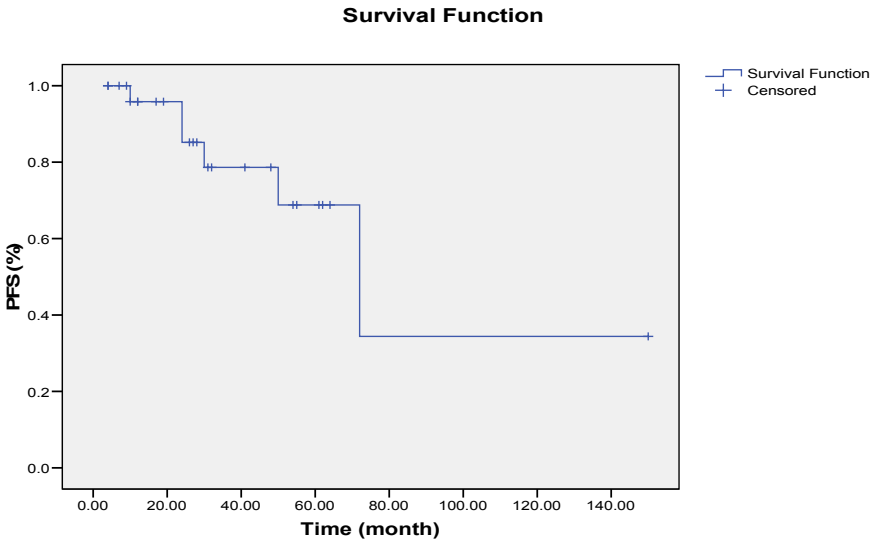

Fig. 3. PFS of all the studied population

3.2 Predictors of Survival

3.2.1 Stage

The M stage of MB at diagnosis significantly affected both OS and posterior fossa PFS (p=0.01 and 0.05 respectively) by univariate analyses. On multivariate analysis, M stage significantly affected OS only (p=0.00).

3.2.2 Surgical resection extent

Incomplete resection predisposed to both posterior fossa relapse and decreased overall survival by univariate analyses (p=0.01 and 0.04 respectively). The negative impact on OS was confirmed by multivariate analysis (p=0.04).

3.2.3 Postoperative residual disease size

No significant effect of the residual size on OS or PFS was revealed

3.2.4 Hydrocephalus and V-P shunt

The presence of hydrocephalus at initial diagnosis, mandating the insertion of V-P shunt,

was associated with significantly inferior OS by both univariate (p=0.04), and multivariate analyses (p=0.02). However, it had no significant effect on PFS.

3.2.5 Time from excision till start of radiotherapy

The time duration from surgical excision till the start of post-operative radiotherapy significantly affected the OS in both univariate (p= 0.01) and multivariate analyses (P=0.01).However, this detrimental effect was not revealed regarding PFS.

3.2.6 Chemotherapy

Chemotherapy administration did not have any significant effect on PFS or OS (P=0.09 and 0.11 respectively).

3.2.7 Other survival predictors

There was no statistically significant impact of position of the tumor gender, age, main presenting symptoms on OS or PFS.

Table 6 showed the multivariate analysis of different predictors.

At the end of the statistical analysis in 1-3-2016 there was 11 patients (17.7%) still alive, 10 patients (16.1%) dead, and 41 patients (66.1%) whom we could not reach them out.

The defects noticed within some patients' records were none precise reporting of the detailed general condition at presentation, and treatment toxicity.

4. DISCUSSION AND RECOMMENDATION

MB is the most common malignant brain tumor in children; arising predominantly from the cerebellar vermis and majorly affecting children in the first decade of life [10]. Regarding this study, treatment outcome and prognostic factors have been analyzed in 62 MB patients treated with postoperative radiotherapy. Early stage of MB at diagnosis, complete resection, and early initiation of radiotherapy after surgery were identified to be associated with improved outcome. Gender, age, main presenting symptoms, and the position of the tumor were not significant predictors.

In spite of the reported favourability of the prognosis of female gender in medulloblastoma [11-13], our trial as well as others [14,15] reported non significant effect of gender on outcome. However there are interests in evaluating the role of estrogen receptors in medullblastoma course [16].

Contradictory reports about effect of age on MB survival exist. Kumar et al. [17] Stated that adult age had more favourable outcome while smoll [18] reported the opposite. In our study, the age of the patient did not affect the outcome similar to Rieken et al. [1].

In spite of the easy resectability of laterally located tumors, studies regarding the effect of tumor location on survival are contradictory. While Korah et al. [19] and Lai et al. [20] stated that lateral tumor location had favourable impact on outcome, Friedrich et al. [21] stated that lateral tumor location had unfavourable impact on outcome. In our study, location had no effect on outcome.

Table 6. Illustration of the multivariate analyses of different predictive factors

Parameter		B	*P value*	Odds ratio	95% CI of Odds ratio
Stage	M0 N=52		0.003*		
	M1 N=7	-1.779	0.009*	0.169	0.045-0.637
	M3 N=3	-0.62	0.425	0.538	0.117-2.468
Extent of surgery	Complete excision N=31		0.016*		
	Partial excision N=25	-1.332	0.041*	0.264	0.073-0.948
	Just biopsy N=6	-0.49	0.449	0.613	0.173-2.176
Time from surgery till radiotherapy		-0.431	0.011*	0.65	0.467-0.905
Hydrocephalus at diagnosis		0.78	0.022*	2.199	1.23-4.306

In the present study, The M stage of MB at diagnosis significantly affected OS as well as posterior fossa PFS by both univariate and multivariate analysis.This goes in harmony with several results as Nazmy et al. [22], Zhang et al. [23] and Kocakaya et al. [24].

The presence of hydrocephalus mandating the insertion of V-P shunt was associated in our study with significantly inferior OS by univariate and multivariate analyses. This might be attributed to the fact that the probability of insertion of shunts is more with high tumor stage which was proved to be a significant negative survival predictor.

The favourable predictive impact of total resection was revealed in our study as well as other studies [1,23-27].

Concerning the MB pathological types, many available literature stated that the desmoplastic histological variant had a favorable prognostic impact on survival rates [1,17,23]. On the other hand large cell and anaplastic types were proved to have a negative impact on survival [28]. The impact of variability in pathologic types on survival was not analyzed in this study due to limited number of cases in the different pathologic groups.

The duration between surgery and postoperative radiotherapy was found to have an impact on survival in our study coinciding with the literature [29].

Definition of the boost field had been a subject of research, entire posterior fossa versus the tumor bed with a margin. Several studies have been published to support the safety and efficacy of the tumor bed boost, like studies done by Carrie, et al. [30], and Moxon-Emre et al. [31]. However, in our study all patients received the boost on the whole posterior fossa as that agreed with our department protocol at the time of treatment implementation.

Chemotherapy did not have any significant effect on patient outcome in the present study. This may be due to the fact that the group which did not receive chemotherapy was too small (15 patients) to be reliable in comparisons, beside the short follow up periods. However there are a lot of interesting work in literature involving the effect of chemotherapy in both pediatric and adult ages and in variable risk categories. Goldwein [32], Packer [33] and their colleagues reported their encouraging results of prospective application of chemotherapy and low dose CSRT in pediatric ages of low risk (10 and 65 patients respectively). An interesting German randomized, prospective, multicenter trial of Kortmann and his colleagues [34] evaluated another issue which is the role of neoadjuvant chemotherapy in medulloblastoma of pediatric ages. Between 1991 and 1997, 137 patients randomized. They concluded that the resulting toxicity affected the later tolerability of radiotherapy. Rutkauskiene and Labanauskas [35] studied prospectively the effect of adjuvant chemotherapy (lomustine, cisplatin and vincristine) versus no adjuvant in 18 high risk pediatric patients with ages (3-18 years). The survival rates were statistically better in the group of adjuvant chemotherapy. Recently a Spanish group [36] published in 2017 their retrospective analysis of the prognostic factors in MB cases below 14 years age treated between January 1990 and December 2013 and the variability in survival patterns all over the different decades. They concluded that the introduction of chemotherapy was the main cause of improved overall survival in recent years.

It seems that the effect of chemotherapy in adult cases is more confusing. In the late eighties, Brandes et al. [37] started a phase II comparison between low risk and high risk adult MB cases (total number was 36) who received neo-adjuvant chemotherapy followed by radiotherapy and adjuvant chemotherapy. After a median follow up of 7.6 years no significant difference between both groups was revealed. Call et al. [38] retrospectively evaluated prognostic factores in 66 adult MB cases. Adjuvant chemotherapy was not among the statistically significant prognostic factors. Mallick et al. [15] retrospectively evaluated prognostic factors in 31 adult MB partients treated from 2003-2011. Adjuvant chemotherapy exerted no statistical significant impact on survival. Franceschi [39] et al. evaluated retrospectively the effect of adjuvant chemotherapy versus no adjuvant on 43 adult MB patients of average risk treated from 1988-2012. Adjuvant chemotherapy did not significantly affect survival. Kann et al. [40] and Kocakaya et al. [24] highlighted the positive role of chemotherapy in adult MB patients. Kann et al. [40] retrospectively evaluated the role of adjuvant chemotherapy in large number of adult MB. Between 2004-2012, 751 patients were registered, 520 (69.2%) received CRT, and 231 (30.8%) received RT. CRT was associated with superior OS compared with RT alone and so was the conclusion of Kocakaya et al. [24] who

investigated 227 publications from 1969-2013 concerning 907adult MB patients.

Our study concluded that the interval between surgery and the start of radiotherapy could affect negatively the survival. This coincides with the results reported by Abacioqlu et al. [41] who studied retrospectively the prognostic factors in 30 patients treated between 1983 and 2000.

No data concerning shunts complications existed in the records, however infection and bleeding were reported in the literature [42].

5. CONCLUSION

In conclusion, this study highlights the effect of stage, completeness of surgery, and early initiation of adjuvant radiotherapy on the outcome .The difference between the impact of chemotherapy on children MB and adult MB need large prospective trials. New molecular subgroups will support treatment personalization and new targeted therapies.

CONSENT

All authors declare that written informed consent was obtained from patients family as regard publication as well as from our institution.

ETHICAL APPROVAL

Authors have obtained all necessary ethical approval from suitable Institutional Committee.

ACKNOWLEDGEMENTS

This work was supported by Mr. Tamer Aly, the head of the patient file Archive of Clinical Oncology Department, Mansoura University, Egypt.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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