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ORIGINAL ARTICLE

Outcomes of Surgery and Craniospinal Radiotherapy for Adult Patients with Medulloblastoma

Zeliha GÜZELÖZ, Zümre ARICAN ALICIKUŞ, Oğuz ÇETİNAYAK, Fadime AKMAN

Department of Radiation Oncology, Dokuz Eylül University Faculty of Medicine, İzmir-*Turkey*

OBJECTIVE

The aim of the present study was to evaluate treatment outcomes for adult patients with medulloblastoma who received craniospinal irradiation following surgery at Dokuz Eylül University Radiation Oncology Department.

METHODS

Twelve patients were evaluated retrospectively. Median age was 31 years (range: 18–55 years). According to Chang staging system, 3 (25%) of the patients were T1, 2 (17%) were T2, 5 (42%) were T3, and 1 (8%) was T4; 1 patient could not be staged due to inadequate preoperative imaging. Tumor location, stage, presence of residual disease, duration between surgery and radiotherapy (RT), age, and sex were evaluated as prognostic factors. Statistical analyses were conducted using Kaplan-Meier method and SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Median dose was 36 Gy (range: 32–44 Gy) to craniospinal field and 54 Gy (range: 50–56 Gy) to primary tumor location. Median follow-up time was 62 months (range: 4–212 months). Five-, 10-, and 15-year overall survival rates were 79%, 63%, and 63%, and 5-, 10- and 15-year progression-free survival rates were 63%, 63%, and 63%, respectively. No statistically significant prognostic factor was found for survival rate. Three (25%) patients developed serious hematological toxicity during RT course. No grade 3 or 4 late side effect was observed.

CONCLUSION

Despite the limited number of cases, results are consistent with the literature. Evaluation of features of this rare disease requires studies with larger number of.

Keywords: Craniospinal; medulloblastoma; radiotherapy.

Introduction

Medulloblastoma is one of the primitive neuroectodermal tumors (PNET) that derive from the ectodermal layer.[1] It is one of the rare tumors of central nervous system tumors in adults. It is most frequently seen between ages 20–40. The incidence has been reported as 0.5/100.000.[2–4] The most common histological type is desmoplastic neuroblastoma. Gross total resection is recommended for all cases without diffuse disease. The standard therapeutic approach is craniospinal radiotherapy (RT) initiating one month after the surgery.[5]

According to current literature, 5 year survival rates in adult patients with medulloblastoma (MB) range

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Dr. Zeliha GÜZELÖZ
Tepecik Eğitim ve Araştırma Hastanesi,
Radyasyon Onkolojisi Kliniği,
İzmir-Turkey
E-mail: zelihaguzeloz@yahoo.com

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between 63% and 84%.[6] The most important factors that effect survival are age, type of resection (total-subtotal-biopsy), presence residual tumor and malignant cells in cerebrospinal fluid (CSF).[7]

In this study, treatment outcomes for adult patients with medulloblastoma who received craniospinal irradiation following surgery in Dokuz Eylül University Radiation Oncology Department were evaluated retrospectively.

Materials and Methods

Patients, diagnosis and staging

In our study, 12 patients who received craniospinal RT following surgery (subtotal/ gross total resection) were evaluated. Median age was 31 (18–55), and female/ male ratio was 1/3.

Seven patients had preoperative magnetic resonance imaging (MRI). Tumor location was cerebellar in 8 (67%) patients, vermis in 3 (25%) patients, supratentorial in 1 (8%) patient. Supratentorial tumor was projecting toward sylvian fissure from left temporal region.

Gross total resection was performed in 10 (83%) patients, and subtotal resection was performed in 2 patients; residual tumor was detected in 6 patients (50%) at postoperative MRI. According to Chang staging system, 3 (25%) of the patients were T1, 2 (17%) were T2, 5 (42%) were T3, and 1 (8%) was T4; 1 patient could not be staged due to inadequate preoperative imaging. All patient were diagnosed with medulloblastoma in pathological examination, and desmoplastic medulloblastoma was identified in 3 of the patients. While cerebrospinal fluid examination could not be performed in 2 patients, no malignant cells were detected in the CSF of the remaining 10 patients (Table 1).

Postoperative neurological performance scores[8] were 3 in 3 (25%) patients, 2 in 1 (8%) patient, 1 in 8 (67%) patients. Karnofsky Performance Scores were 60 in 2 (17%) patients, 70 in 1 (8%) patient, 80 in 2 (17%) patients, and 90 in the remaining 7 (58%) patients.

Radiotherapy

All patients were immobilized at prone position using forehead-chin rest and orfit head mask during radiotherapy. Craniospinal RT was performed in opposite parallel two lateral cranial and two different spinal fields (dorsal and lumbosacral) with appropriate photon energy levels (6–18 MVX, Co-60), followed by opposite parallel boost at posterior fossa. Planned doses were 36 Gy (1.8–2 Gy/fraction, 5 fractions/week) at cranial and spinal fields, and 54 Gy at posterior fossa.

Table 1 Patient and surgery information

	Number of patients	
	n	%
Gender		
Female	3	25
Male	9	75
Surgery		
Subtotal resection	2	17
Gross total resection	10	83
Tumor Location		
Cerebellum	8	67
Vermis	3	25
Supratentorial	1	8
Pathology		
Desmoplastik variant	3	25
Others	9	75
Chang staging system		
T1	3	25
T2	2	17
T3	5	42
T4	1	8

Statistical analysis

Statistical analyses were carried out with Kaplan-Meier method using SPSS-15 software. Tumor location, stage, presence of residual disease, duration between surgery and RT, age, and sex were evaluated as prognostic factors. Overall survival was calculated as the time beginning from the diagnosis until the last follow-up or death; progression-free survival was calculated as the time beginning from diagnosis until progression.

Results

Median duration between surgery and RT in patients who applied for RT was 38 (20–220) days. Median follow-up duration was 64 (4–212) months. Fraction doses at cranial and spinal fields ranged between 1.8–3.6 Gy (median is 1.8 Gy); total median doses were 36 (32–40) Gy at cranial field, 54 (50–56) Gy at primary tumor location, and 36 (32.4–44) Gy at spinal field. One patient with supratentorial tumor received adjuvant chemotherapy (CT). Five, 10, and 15-year overall survival rates were 79%, 63%, and 63%, and 5, 10 and 15-year progression-free survival rates were 63%, 63%, and 63%, respectively (Figure 1, 2). Recurrence was detected in 3 (25%) patients at 39th, 47th, and 57th months. These patients were treated with CT, surgery, and surgery+ CT, respectively. The patient who was treated with surgery died 2 months after recurrence because of sepsis that

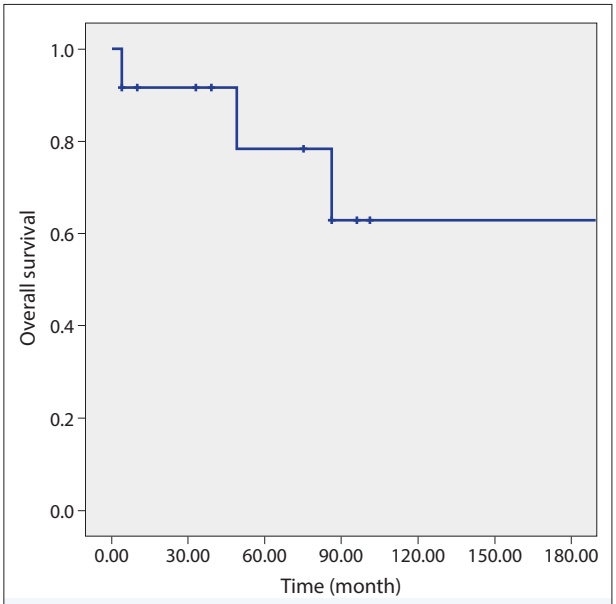

Fig. 1. Overall survival table.

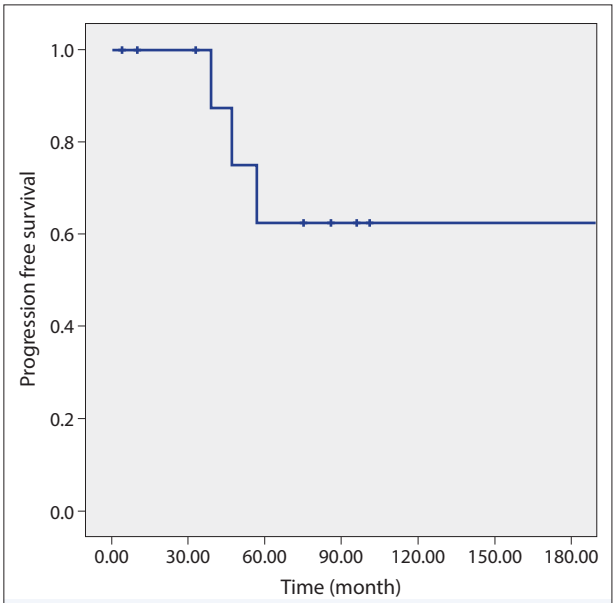

Fig. 2. Progression free survival table.

developed at early period. The patient who was treated with CT+surgery died 26 months after recurrence. The patient who was treated with CT was followed up for 35 months after recurrence without any problems. Due to limited number of patients, a statistically significant prognostic factor effecting the survival rates could not be determined. Three (25%) patients developed severe acute hematological toxicity during RT; none of the patients developed late grade 3–4 side effects.

Discussion

MB occurs most commonly in childhood (median age is 6).[9] It is one of the rare tumors of central nervous system in adults. The tumor is located at the posterior fossa. Craniospinal involvement is observed as in the rates of 30–35%.[9] MRI or computed tomography is used for diagnosis. MRI is preferred because of its superiority for demonstrating the relation to neighboring tissues and diffusion of the tumor.[10] In our study, craniospinal MRI was performed in 7 patients for this reason. Gross total resection is recommended for all patients without diffuse disease. Type of resection, residual amount, cerebrospinal fluid involvement are prognostic factors. While patients who had complete or near complete resection, who had residual tumor smaller than 1.5 cm^2, and who do not have CSF involvement are regarded to have standard risk, those who had subtotal resection or biopsy, who had residual tumor larger than 1.5 cm^2, and who have CSF involvement are regarded to have high risk.[7] In our retrospective study, images of some patients could not be obtained; therefore, risk assessment could not be made.

In adjuvant RT, our clinical target volume covers whole craniospinal axis. Craniospinal RT is a difficult treatment modality making use of complex techniques. Since craniospinal axis containing the brain, spinal cord, and meningeal structures, which are defined as clinical target volume, have an irregular structure, technical difficulties arise during planning phase.[9] Craniospinal axis is irradiated with 36 Gy in high risk patients. Then, it is recommended to increase the dose to 54–55.8 Gy at posterior fossa. In case of intracranial or spinal metastasis, the dose should be increased to 45–50 Gy in spinal metastasis and to 50–54 Gy for cranial metastasis.[11] In our study, median doses were 36 (32–40) Gy at cranial field, 54 (50–56) Gy at primary tumor location, and 36 (32.4–44) Gy at spinal field, similar to other reports in literature.

With the advances in technology, intensity modulated radiotherapy and volumetric modulated arc treatment have been shown to be superior to three dimensional conformal therapy for the treatment of MB today, due to more homogenous doses at target volume and lower dosage to organ at risk.[12,13] It is reported that heart, inner and middle ear, temporal lobe doses are lower in proton treatment which is known to be a more advanced technique, compared to treatments with photons and electrons.[14,15]

Germanwala et al. reported that boost dose at posterior fossa in the presence of residual tumor could be

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performed with gamma knife. There were less side effects, and higher doses could be attained by this way.[16] There has been a dose deduction in standard risk patients in order to decrease long-term morbidity related to RT. There are studies suggesting that spinal dose could be deduced to 23.4 Gy in low risk pediatric patients with MB; however, this concept is controversial for adult group of patients.[17] In one study by Packer et al., pediatric patients with standard risk were administered weekly vincristine concurrently with 24.3 Gy irradiation at craniospinal field, and dose at posterior fossa was completed to 55.8 Gy with boost. Five year progression-free survival in these patients who received adjuvant vincristine, CCNU, cysplatine CT was determined as 79%.[18] In the series of Carrie and Padovani, adult patients were administered concurrent chemo-RT. In Carrie's study involving 30 patients, 7 patients were administered CCNU-vincristine concurrently with RT. Five and 10 year overall survival rates were reported as 58.5% and 41%, respectively.[19]

Adjuvant RT should be initiated within 28–30 days following surgery, and the treatment should be continued without any interruptions if possible. In International Society of Paediatric Oncology (SIOP) PNET-3 study, it was stated that interruptions during treatment affected overall and disease-free survival adversely.[20] In their study involving adult patients with MB, Abacıoğlu et al. reported the median duration of interval between surgery and RT as 31 (12–69) days. Five year disease-free survival rates were found as 0% for patients who started their treatment earlier than 3 weeks, 85% for patients who started their treatment between 3 to 6 weeks, and 75% for patients who started their treatment after 6 weeks.[21] In our study, the median duration to initiate RT after surgery was 38 (20–220) days. Any statistically significant effect of this duration on survival rates could not be analyzed due to limited number of patients in our study. In 3 patients who had progression, the duration between surgery and RT was 25, 47 and 39 days. It is known that the administered adjuvant CT contributes to survival in pediatric patients with MB who have adverse prognostic factors.[22] The importance of adjuvant CT for adult MB cases is controversial. CT does not have any contribution on survival in low risk patients. Moreover, adult patients do not show good tolerance against pediatric CT regimes.[23] In their study involving 32 patients, Herrlinger et al. found that adjuvant vincristine, CCNU, cisplatin or methotrexate, cisplatin chemotherapies contributed to survival, although it was not statistically significant.[24] In our study, adjuvant CT was administered in one patient with supratentorial tumor. There was no recurrence or distant metastasis in the follow-up after adjuvant RT or CT.

Recurrences develop mostly in posterior fossa.[23–25] A review of recurrence patterns indicated that recurrences occur mostly within 2 years in pediatric group.[26,27] This duration is longer for adult patients. Chan et al. reported median duration before recurrence as 26 months. It was stated that 29% of the recurrences occurred 5 years after treatment.[25] In our study, recurrence was detected in 3 patients at 39th, 47th, and 57th months, found at the primary tumor location. Those patients died at 2nd and 26th months after recurrence. Durations before recurrence in our patients were longer than the durations reported in the literature. Systemic involvement is seen in 5% of patients. Most frequently bone and bone marrow involvements are observed.[28] In our patients, no distant metastasis was detected.

According to evaluation of all patients in our study, 5, 10, and 15 year overall survival rates were 79%, 63%, and 63%, respectively; 5, 10, and 15 year progression-free survival rates were 63%, 63%, and 63%, respectively. These results are in conformity with the results reported in literature. According to a report published in 2012 by Lai et al., which reviewed 13 studies, 5 and 10 year general survival rates varied between 63–84%, and 52–73%, respectively; 5 year progression-free survival rates varied between 62–80%.[6] In those studies where median follow-up durations ranged between 3.5 to 6.6 years, there were no results for 15 year survival rates.

Age is an important prognostic factor for childhood MB. However, it is not regarded as an important parameter for adult age group; moreover, there is evidence that increasing age is favorable with regard to survival.[29] It is thought that adult women with MB have better survival outcomes. Lee et al. determined the 5 year survival rate as 92% for females and 40% for males.[29] In our study, age and sex factors were not found significant with regard to survival.

Most of the studies did not yield a statistically significant prognostic factor. In the study by Padovani et al. which had the greatest number of patients, metastasis, postoperative performance, central nervous system involvement were determined as factors that are important for prognosis;[19] other prognostic factors were determined to be M stage and duration before initiation of postoperative RT in the study by Abacıoğlu et al.[21] location of tumor in the study by Menon et al.[30] type of surgery, RT and histology in the study by Lai et al.[31] gender in the study by Riffaud et al.[32]

In our study, we think we could not find a statistically significant prognostic factor because of the limited number of patients.

There are studies reporting that the biological markers, TrkC and C-MYC are independent predictive factors for medulloblastoma and primitive neuroectodermal tumors.[33,34] MDM2 overexpression is thought to be associated with shorter survival.[35] However, we could not evaluate these parameters in our study, since these biological markers are not routinely tested in our center.

Because adult MB is a rare pathology, studies in literature include limited number of patients and are retrospective. Although surgery and craniospinal RT is the standard treatment, its importance in adult MB is still controversial. As a conclusion, despite the limited number of cases in our study, our results are in conformity with other results in literature. However, in order to clarify prognostic properties and effectiveness of adjuvant treatments such as CT in this rare disease, studies including larger number of patients are required where cases would be collected at multiple centers.

Disclosure Statement

The authors declare no conflicts of interest.

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