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ORIGINAL PAPER

Medulloblastoma/primitive neuroectodermal tumor in adults: prognostic factors and treatment results: a single-center experience from Turkey

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Abstract We performed retrospective review of 29 adult patients with cerebellar medulloblastoma/primitive neuroectodermal tumor (PNET) who received craniospinal radiotherapy in Ankara Oncology Hospital between years 2000 and 2005. All patients were operated followed by craniospinal irradiation; 11 of 29 patients also received chemotherapy. All patients had no distant or spinal metastases at the time of diagnosis. Median follow up time was 26 months. Progression-free survival was 86% at 2 years, 55% at 5 years. Mean progression-free survival was 25 months in patients with PNET; 61.4 months in patients with medulloblastoma ($P = 0.0016$). Mean survival was 61.33% months in patients <25 age, 38 months in patients >25 age. ($P = 0.04$). Overall mean survival was 59.80 months in patients who received chemotherapy and 41.4 months in patients who did not have chemotherapy ($P = 0.15$). Cranial relapses were observed in 3 of 29 patients, and 3 of 29 patients had distant metastases. The mean time to cranial recurrence was 19 months; to distant metastases was 18 months. In conclusion, adult patients with PNET have worse survival rates than patients with medulloblastoma, like in childhood patients. Patients younger than 25 years of age also had statistically significant better survival.

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Introduction

Adult medulloblastoma constitutes 15–20% of all medulloblastomas and 1% of all adult cranial tumors. Median age of these patients is 25. According to WHO classification medulloblastoma, ependymoblastoma, and PNET are embryonal tumors. Common clinical behaviour of these tumors is their tendency to spread to CSF (cerebrospinal fluid) [1–5]. Two important medulloblastoma variant are defined as classical and desmoplastic types. Primary localization of medulloblastoma is posterior fossa. The incidence of CSF spread is 10–15% at diagnosis, but metastatic disease has been noted in more than 50% of autopsies of patients who died of recurrent disease. Systemic metastatic incidence rate is about 5%; especially to lymph nodes and bones [1–6].

The 5-year overall survival rates range from 58 to 84% [1, 5] that are comparable to those of childhood medulloblastoma patients, 5-year-progression free survival rates range from 40% to 61% (1, 4, 5). Poor risk adult medulloblastoma patients have one or more of the following clinical factors: >25% of tumor remaining after resection, brainstem invasion, tumor cells present in the CSF, or evidence of distant metastases.

PNET is less curable than medulloblastoma; in spite of has been classified with the same group of the medulloblastoma [7–11]. Local or regional recurrences are seen in many patients in spite of craniospinal radiotherapy [7, 8]. Chemotherapy is especially the part of multimodality treatment approach.

Patients and methods

About 29 patients received adjuvant craniospinal radiotherapy between years of 1998 and 2005. Pathological results were medulloblastoma in 23 patients and PNET in six patients.

Complete macroscopic removal was achieved in 18 patients (16 patients in medulloblastoma, three patients in PNET); subtotal removal in nine patients.The extent of resection could not be determined in two patients. 29 patients received craniospinal irradiation with 6 MV linear accelerator.The median irradiation dose was 40 Gy. for the whole brain; 36 Gy for spine and 10–14 Gy boost for posterior fossa.

Eleven patients received 4–6 cycle PVC (procarbazin 150 mg, vincristin 2 mg, CCNU 120 mg) chemotherapy (three patients in PNET, eight patients in medulloblastoma). After completion of treatment, patients had check-up with physical examination, posterior-anterior chest X-ray and cranial- spinal magnetic resonance imaging.

Statistical methods

Progression-free survival was estimated with Kaplan–Meier method and comparable tests were performed with log-rank test. Progression-free survival was estimated from the date of surgical resection until the date of tumor progression. Median survival was not reached, because of insufficient number of progression.

Results

Of 29 patients, 19 were male. Patients' characteristics were shown in Table 1. Tumor histology were medulloblastoma in 22 patients; PNET in 6 patients and medulloblastoma with high-grade ganglioma in one patient. Medulloblastoma were classical in 15 patients; desmoplastic in six patients and neuroblastic in one patient.

Primary presenting symptoms were headache, nausea-vomiting, ataxia in 23 patients, motor dysfunction in two patients, seizure in two patients and dyplopia in two patients. Ean symptom duration before diagnosis was 5.4 months (range, 2–120 weeks). Tumor size was <5 cm in 20 patients; >5 cm in 6 patients. Tumor size could not be defined in three patients. About 11 patients received PVC (procarbazin, vincristin, CCNU) chemotherapy regimen (three patients in PNET, eight patients in medulloblastoma).

Median follow time was 26 months (range, 4–69 months). Progression-free survival was 86% at 2 years, 55% at 5 years (Fig. 1). Mean survival 25 months in patients with PNET; 61.43 months in patients with medulloblastoma ($P = 0.0016$) (Fig. 2). Mean survival was 61.3 months in patients <25 age, 38 months in patients >25 age ($P = 0.04$) (Fig. 3).

Cranial recurrences were observed in three patients. Three patients developed distant metastases during follow-up and two patients died. Mean time to recurrence was 19 months (range, 4–26 months). Mean time to distant metastases was 18 months (range, 8–23 months). Distant metastases sites were bone in two patients, lung in one patient. Cranial recurrence was observed in one patient after 9 months of diagnosis of lung metastases.

Table 1 Common characteristics of patients

	No.	%
Sex		
Female	10	34
Male	19	66
Histopathology		
PNET	6	21
Medulloblastoma	23	79
Chemotherapy		
No	11	38
Yes	18	62
Operation		
Gross total	18	62
Subtotal	9	31
Unknown	2	7
Tumor dimension		
>5 cm	20	69
<5 cm	6	20
Unknown	3	11
KPS		
>70	23	79
<70	6	21

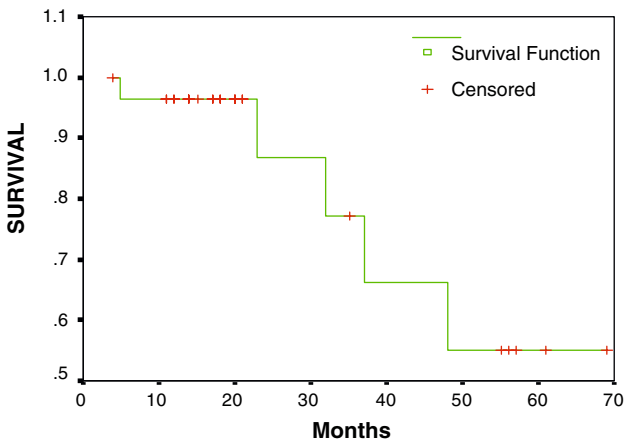

Fig. 1 Five-years progression-free survival in patients with medulloblastoma/PNET

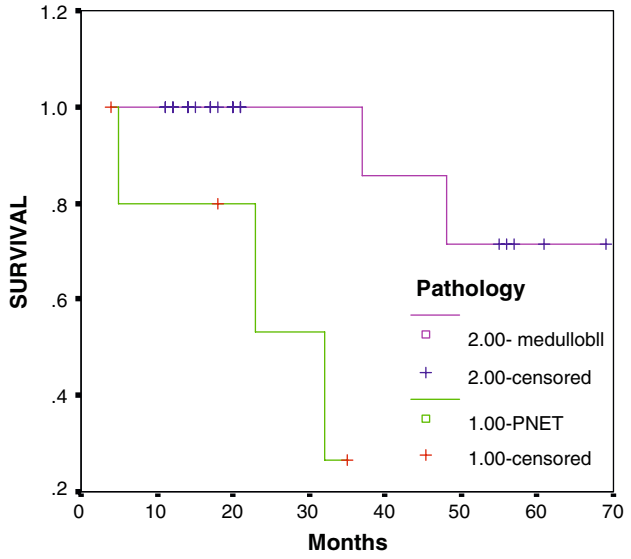

Fig. 2 Comparable progression-free survival in patients with PNET or medulloblastoma

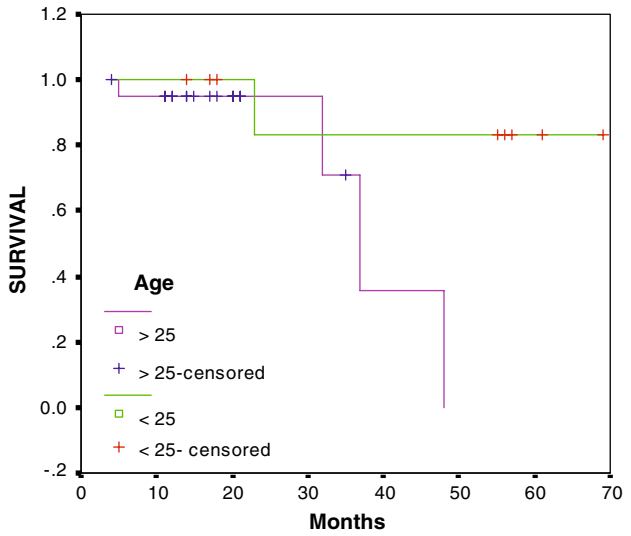

Fig. 3 Progression- free survival according to age

Discussion

We evaluated 22 medulloblastomas and 6 PNET adult patients retrospectively. Median follow up time was 26 months (range, 4–69 months). Progression-free survival was 86% at 2 years, 55% at 5 years. Mean survival was 25 months in patients with PNET; 61.4 months in patients with medulloblastoma ($P = 0.0016$). We found statistically significant survival advantage in medulloblastomas compared to patients with PNET. In univariate analysis, we found better survival in patients younger than 25 years of age. We also found statistically non-significant prolonged survival in female patients and the patients who received adjuvant.

The two main medulloblastoma types are classical and desmoplastic. Unlike tumors arising in childhood, adult medulloblastomas have higher incidence of the desmoplastic type (30%) compared to the classic histologic variant [12–14]. In this study, six patients (26%) had desmoplastic type. In childhood, medulloblastoma usulally arise from midline cerebellar localization. However, adult medulloblastomas have higher incidence of lateral cerebellar location compared to the midline (30–40%). In this study tumor location was cerebellar in 21 patients with medulloblastoma; frontal in one patient with medulloblastoma—high-grade ganglioma. Tumor location was supratentorial in three patients and infratentorial in three patients with PNET.

Primary treatment modality in medulloblastoma/PNET is tumor resection. Due to the risk of the CSF dissemination, craniospinal irradiation is given postoperatively. Adjuvant chemotherapy is especially the important part of treatment in PNET patients. Unlike PNET patients; chemotherapy is reserved for recurrent or progressive disease in adult medulloblastoma. In this study, craniospinal radiatherapy was administered postoperativelly to all patients and, adjuvant chemotherapy was administered in 11 patients (38%).

Some important poor risk factors have been defined in adult medulloblastoma patients as >25% of tumor remaining after resection, brainstem invasion, tumor cells present in the CSF, or evidence of distant metastases. Prados and colleagues evaluated retrospectively poor risk (26 patients) and standard risk (21 patients) adult medulloblastoma patients. They found that 5-year overall survival and disease free survival rates significantly differed between the risk groups (overall survival: 81% vs 54%; disease free survival: 58% vs 38%) [1]. Another study reported better progression-free survival at 5 years in low risk adult medulloblastomas [15]. These findings supporting treatment decisions may also be modified according to risk groups in adult medulloblastoma like in childhood. In this study, 29 adult medulloblastoma/PNET patients evaluated retrospectively who had no distant or spinal metastases at diagnosis.

Some individual prognostic factors have been evaluated in adult medulloblastoma patients. Unlike in childhood medulloblastoma; most of these factors have not been found to be significantly predictive in adults. Male gender was reported to be significantly predictive of worse survival [2]. Authors found 5-year survival rate of 92% in female patients, 40% in male patients. Tabori et al. reported better survival female patients in adolescents [13] .In our study, we did not find any progression in female patients in spite of statistically nonsignificant (5-year-progression-free survival is 100% in female patients, 43% in male patients), ($P = 0.12$).

Age is a very important prognostic factor in childhood medulloblastomas whereas it has not been found to be significantly predictive in adult patients. However, one study reported survival advantage in older patients [2]. In our study, mean survival was 61.3 months in patients younger than 25 years old, 38 months in patients >25 age ($P = 0.04$).

Contrary to childhood medulloblastoma, the optimal use of adjuvant chemotherapy is unclear in adults and there are different chemotherapy regimens reported in the literature. Prados and colleagues reported statistically significant survival advantage in patients who received chemotherapy as compared to the patients who did not receive (1). However, this benefit has not been found in other series [2, 4, 6, 14]. No benefit of concomitant chemotherapy was demonstrated in one study [4]. Herrlinger et al. reported non significant trend to prolonged survival with adjuvant chemotherapy in adult patients ($P = 0.068$) [12]. In our study, mean survival was 59.8 months in patients who received chemotherapy; 41.4 months in patients who did not received chemotherapy ($P = 0.15$).

In pediatric patients, PNET has been reported to be less curable than medulloblastoma [9, 11]. Local or regional recurrences are seen in significant part of patients with PNET in spite of adjuvant chemotherapy [7, 8]. Chemotherapy especially is the important part of the treatment. In one study, 1-year survival rate has been reported to be 10% [10]. Some reports reported 5 year survival rate of 20–25% [9]. In our study, 2-year progression-free survival was 86%; 5-year progression-free survival is 55%. While progression- free survival is 25 months in patients with PNET; 61.4 months in patients with medulloblastoma ($P = 0.0016$). Our results as I line with the literature showed that PNET in adult patients, like in childhood patients have worse prognosis than patients with medulloblastoma. Furthermore, in our study treatment failure rate can be related to the fact that half of PNET patients didn't receive chemotherapy.

Late recurrences are more common in adults than in children. In general, 75% of all childhood medulloblastoma recurrences were seen more than 2 years [2, 9]. In one study, it has been reported that 59% of all recurrences were seen more than 2 years after completion of treatment. Late recurrences as late as 14 years after treatment have been reported. In our study, cranial recurrences were seen in three patients; distant metastases were seen in three patients. Distant metastases locations were bone two patients; lung in one patient. The mean time to cranial recurrence was 19 months; the mean time to distant metastases was 18 months. In our study, median follow time was 26 months.

In conclusion, adult patients with PNET have worse survival rates than patients with medulloblastoma, like in childhood patients. Patients younger than 25 years of age also had statistically significant better survival.

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