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Pathologic Characteristics and Treatment Outcome of Patients with Malignant Brain Tumors: A Single Institutional Experience from Iran

Abdolazim Sedighi Pashaki[*], Ehsan Akbari Hamed[*], Kamal Mohamadian[*], Mohammad Abassi[**], Afsane Maddah Safaei[*♦], Mohammad Babaei[***], Mohammad Hadi Gholami[****], Ali Reza Khoshghadam[****]**

*Mahdieh Department of Radiation Oncology, Hamadan, Iran
**Hamadan University of Medical Sciences, Hamadan, Iran
***Tehran University of Medical Sciences, Tehran, Iran
****Physicist, Mahdieh Department of Radiation Oncology, Hamadan, Iran

Abstract

Background: Central nervous system tumors account for 2%-5% of all malignancies in humans. These tumors account for 2% of all pediatric cancers. The worldwide incidence of primary central nervous system tumors is estimated at 3.9 (males) and 3.2 (females) per 100000 person-years. The incidence of brain tumor cases has been reported as 3.67% of all malignancies and 4% of all cancer mortalities in Iran. The five most common histological types of brain tumor in Iran according to different case studies are; meningioma, astrocytoma, glioblastoma, pituitary adenoma and ependymoma. The aim of this study is to determine the histopathological pattern and characteristics of patients with brain tumors who have referred to the Mahdieh Radiotherapy Department, Hamadan, Iran.

Methods: This descriptive, retrospective study was performed at the Mahdieh Radiotherapy Department, between 2005 and 2012. We included 220 patients who referred to the Radiotherapy Department with diagnoses of primary brain tumor in this study.

Results: Between 2005 and 2012, we treated 220 new cases of primary brain tumor at Mahdieh Radiotherapy Department. The mean age at diagnosis was 39.95±15.48 years with a median age of 39 years. Patients' ages ranged from 4 to 75 years. Among the 220 patients, 138 were male and 82 were female with a male to female ratio of 1.68. For most tumors there was a male predominance, with the exception of meningioma (M/F: 0.23), ependymoma (M/F: 1) and pituitary adenoma (M/F: 0.6). Astrocytomas, glioblastomas, high grade meningiomas and oligodendrogliomas were the four most common pathologies treated in this department. The best treatment results were achieved in patients with astrocytomas.

Conclusion: The present study is a retrospective radiotherapy centre-based study designed in a pioneer radiotherapy centre in Western Iran, not a prospective population study. These data have provided a baseline for further epidemiological studies. Our encouraging results in radiotherapy treatment of primary malignant tumors clearly highlight the benefits of definitive or postoperative radiation.

Keywords: Malignant brain tumor, Surgery, Radiotherapy, Outcome

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♦Corresponding Author:
Afsane Maddah Safaei, MD
Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98-021-61192518
Email: Afsan1980@ymail.com

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Introduction

Central nervous system (CNS) tumors account for 2%-5% of all malignancies in humans and 2% of all pediatric cancers. The incidence of primary CNS tumors has been estimated as 3.9 (males) and 3.2 (females) per 100000 person-years worldwide. Nevertheless, the incidence of primary CNS tumors ranges from 2.1 to 5.8 per 100000 individuals worldwide and is higher in developed countries. The mortality from brain tumors vary from 2.3 in South America to a high of 6.8 per 100.000 people in Japan.[1] In Iran, the incidence of brain tumor cases has been reported as 3.67% of all malignancies and 4% of all cancer mortalities.[2]

The five most common histological types of brain tumors in Iran according to different series are meningiomas, astrocytomas, glioblastomas, pituitary adenomas and ependymomas. Astrocytomas and glioblastomas are the most common malignant brain tumors.[3]

International differences in the frequency of brain tumors suggest a role for environmental factors. Little is known about risk factors or causative agents of brain tumors. Epstein-Barr virus and history of irradiation in association with primary CNS lymphoma and meningioma have been reported although there is scant evidence for an association between oncogenic virus SV-40 and ependymoma.[4] Meningioma is reported to have a relationship to sex hormones.[5]

Surgical procedures to treat brain malignancies can be summarized as biopsy for diagnosis only, resection for cure, surgical debulking for management of mass effect related symptoms, additional resection for recurrent tumors or to manage the effects of symptomatic necrosis.[6]

The indications for postoperative radiation and radiotherapy techniques differ according to tumor grade and histopathological type. The most commonly used radiation techniques in the treatment of brain tumors are partial brain irradiation and, less frequently, whole brain or craniospinal irradiation.[7]

The aim of this study is to determine the histopathological pattern, characteristics and treatment outcome of patients with brain tumors who referred to the Mahdieh Radiotherapy Department, Hamadan, Iran. All patients enrolled in this study had pathologically proven brain tumors and were candidates for postoperative or definitive radiotherapy according to current standard guidelines.

Materials and Methods

Patients

This descriptive, retrospective study was performed at the Mahdieh Radiotherapy Department - the first radiotherapy center in Western Iran. The study was conducted between 2005 and 2012. During this time, a total of 220 patients who attended the Radiotherapy Department and had diagnoses of primary brain tumors were included in the study.

Data abstracted from the patients' clinical records included age at the time of diagnosis, sex, histological diagnosis of the tumor, tumor location, radiotherapy protocol and dose, imaging information, time of last follow up and patients' status (alive or expired) at the time of data abstraction.

Treatment policy and follow up

All patients underwent radiotherapy after surgery or biopsy. The definitive treatment was radiotherapy in those with brain stem tumors who were not candidates for biopsy. The extent of surgery was defined as: complete resection (resection of more than 95% of the tumor), subtotal resection (resection of 50%-94% of the tumor), partial resection (any surgical debulking less than the subtotal resection) and biopsy only. Patients were simulated and treated using a thermoplastic face mask for immobilization. A computerized tomography (CT) scan of the head was obtained after which images were transferred to a core plan treatment planning system. Patients were treated with a Siemens linear accelerator in the Radiotherapy Department with the dose delivered according to standard recommendations for primary malignant brain tumors.

MRIs were obtained at 4-6 weeks post-

radiation for response evaluation and for comparison with the post-surgery MRI. MRIs were obtained every 6-12 months thereafter. Response was defined using the MacDonald criteria. The MacDonald criteria evaluate responsiveness as a 30% decrease in the largest tumor area. Progressive disease is a 25% increase in the largest tumor diameter. Early radiological progression was defined as any radiological progression from baseline to 4-6 weeks post-radiotherapy. Patients with clinically stable disease for at least six months post-radiotherapy were considered to have pseudo-progression, particularly in cases of glioblastoma patients.

Statistical analysis

Clinical and pathologic variables were analyzed by SPSS-18 statistical software. Time to event distribution was estimated by the Kaplan-Meir method. $P<0.05$ was considered significant.

Results

Between 2005 and 2012, there were 220 new cases of primary brain tumors treated at Mahdieh Radiotherapy Department, an average of 32 cases per year. Among the 220 patients, 138 were male and 82 were female (male to female ratio: 1.68). The mean age at diagnosis was 39.95±15.48 years with a median age of 39 years and a range from 4 to 75 years. The mean age did not significantly differ between sexes. Patients with medulloblastomas were significantly younger at diagnosis compared with other brain tumors ($P<0.05$). Patients with glioblastoma multiforme were significantly older in comparison to patients with grade 2 and 3 astrocytoma, ($P<0.05$).

The most common clinical presentations in patients referred for postoperative or definitive radiation were headache (63.18%), anorexia (45.4%), seizure (54.5%), hemiparesis or hemiplegia (36.3%) and vomiting (48.6%). Most patients (68%) had more than one clinical presentation.

In patients referred for radiotherapy, the rate for subtotal resection was 4.5% and for partial resection it was 77.2%. There were 12.7% of patients who only underwent a biopsy and 5.4% had no biopsy or additional surgery. Patients with brainstem tumors or pituitary hormone secreting adenomas comprised the group who received definitive radiation without histological confirmation. Table 1 shows the frequency distribution of different types of brain tumors treated in our department by age and male to female ratio.

All patients underwent radiotherapy with or without chemotherapy. Table 2 shows the mean dose of radiation and median overall survival for these patients. There was a significantly higher median survival for astocytoma (grade 2) and oligodendrogliomas ($P<0.05$; Figure 1).

Magnetic resonance (MR) imaging was obtained 4-6 weeks post-radiotherapy. The rate of partial response was 60.9%, for stable disease it was 11.36% and progression was seen 22.2% of patients. Patients with brainstem glioma and pituitary adenomas mostly had stable disease at the first follow up imaging study. Progressive disease was significantly found in patients with glioblastoma and high grade astrocytoma.

Discussion

Based on systemic reviews, the incidence of primary brain tumors in Iran is estimated to be 5.69 per 100000; benign and malignant brain tumors are estimated to be 2.95 and 2.74 per 100000. Although the worldwide incidence of brain tumors is estimated to be 3.7 for males and 2.6 for females per 100000, underdeveloped countries report a lower incidence. It seems that the reported incidence of brain tumors is related in part to the economy of various countries. The highest rates of incidence are seen in North America, Australia and Western Europe.[8]

According to the Iranian Annual National Cancer Registration Report in 2009 the incidence of primary brain tumors in Hamadan Province was 1.04 for females and 2.61 for males per 100000 individuals, which was less than the Iranian population.[9] The difference in brain tumor incidence in Iran might be attributed to the role of environmental exposures such as ionizing

Table 1. Histological findings of brain tumors adjusted by sex and age.

Type	N (%)	Age (years)	Male/female ratio	Predominant site
Astrocytoma	75 (34.1)	35±14.55	2.26	Frontal and frontoparietal
Glioblastoma	68 (30.9)	48.9±12.8	1.8	Frontal and parietal
Oligodendroglioma	21 (9.5)	36.7±13.2	1.33	Frontal and frontoparietal
High grade meningioma	16 (7.3)	49.87±10.1	0.23	Frontal
Brain stem tumors	11 (5)	29.18±12.52	1.2	Brain stem
Medulloblastoma	4 (1.8)	15.75±9.74	3	Posterior fossa
Pituitary adenoma	8 (3.6)	33.3±11.6	0.6	Pituitary
Ependymoma	6 (2.7)	35.67±9.81	1	Posterior fossa

radiation, pesticides, electromagnetic features, genetic factors and the age distribution in different provinces.[2,10]

In the current study, the male to female ratio was 1.68 which was comparable to other studies.

According to our results the majority of tumors showed a male predominance with the exception of meningioma (M/F: 0.23), ependymoma (M/F: 1) and pituitary adenoma (M/F: 0.6).

Based on the National Cancer Registry of Iran, the mean age for common pathologies of malignant brain tumors in Iran was 40.2±19.8 years. Of note, the mean age of our patients was 39.95±15.48 years.[10]

The five most common malignant tumors in Iran are astrocytoma, glioblastoma, oligodendroglioma, medulloblastoma and ependymoma. The frequency of malignant tumors in our study compared to registered data from the Iranian literature is shown in Figure 2.[10]

The prevalence of malignant brain tumors

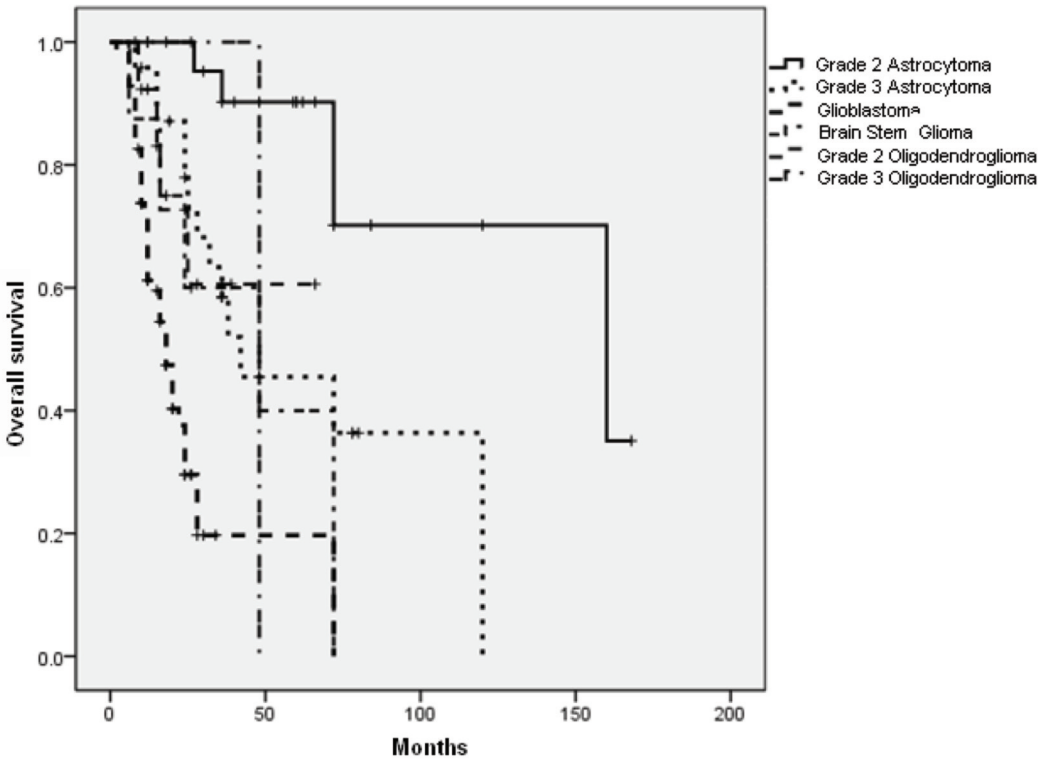

Figure 1. Kaplan Meier survival curves of overall survival categorized according to tumor type.

Table 2. Radiotherapy dosage and median overall survival (OS) adjusted by tumor type.

Type	RT dose (cGy)	Median OS (months)
Astrocytoma	5689±495	42
Glioblastoma	5960±688	18
Meningioma (grades II and III)	5618±310	*
Oligodendroglioma	5845±301.8	21
Brain stem glioma	5720±452	48
Pituitary adenoma	5250±257.6	All survived
Medulloblastoma	5495±430	*

*Only one death was reported among these groups of patients.

treated in our department was comparable to the epidemiology of these tumors, as reported in Iranian literature.[9,10-12]

Despite the fact that meningiomas are the most common brain tumors, only patients with partially resected high grade meningiomas had referred to our radiation department. Thus our results were not reflective of the actual incidence of meningioma in Western Iran.

Pituitary tumors make up approximately 10% of all brain tumors. However in the current study, pituitary tumors have accounted for less than 4% of treated patients (8 adenoma and 1 craniopharyngioma). This lower rate might be related to the use of medical treatment for the most frequent type of pituitary adenoma, prolactinoma, which would decrease the necessity for radiation.[11-12]

Some intracranial tumors occur at all ages, whereas others develop preferentially in childhood. Medulloblastoma is the second most common brain tumor in childhood.[13] According to National Cancer Registry data, the mean age of patients with medulloblastoma in Iran was 15.7±12.4 years which was comparable to our results (15.75±9.74 years).[10] Medulloblastoma was the third most common tumor among patients less than age 20 in our study.

The prognosis for patients with glioblastoma is poor with a median survival of 14 months (5-18 months). The median survival of 18 months for patients with GBM in our experience , is consistent with the maximum level of median survival in GBM patients.

We analysed all potential prognostic factors to evaluate their effect on overall survival in patients diagnosed with glioblastoma and grade 3 astrocytoma. Age ≤50 years, concurrent and adjuvant chemotherapy, and the extent of surgery were significantly related.

The median survival for patients with

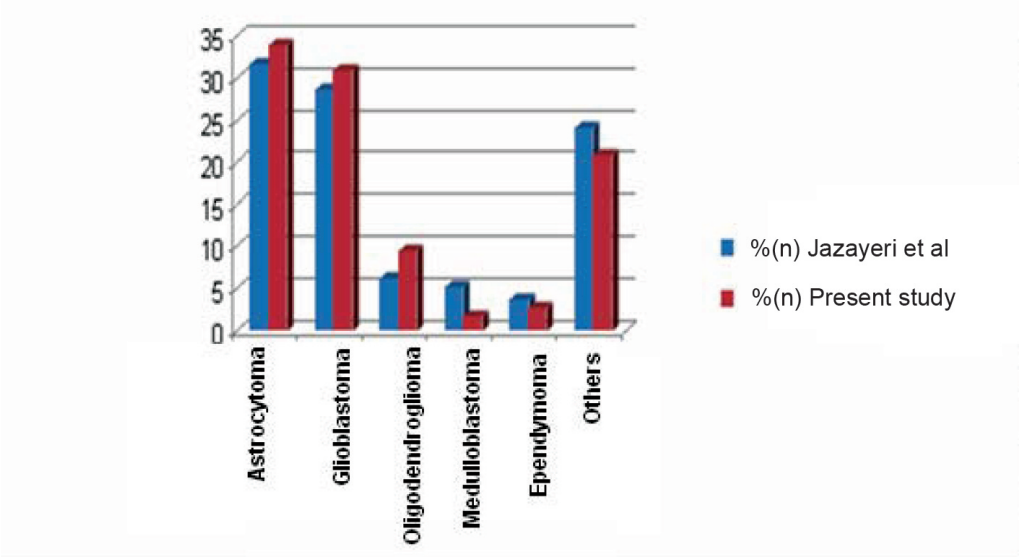

Figure 2. The frequency of malignant tumors in our study compared to registered data from the Iranian literature.

astrocytomas who have been treated with surgery and postoperative radiation is 2.7-8.7 years which supported our results (3.5 years-40 months).[14]

In conclusion, the present study showed the epidemiologic and treatment outcome of patients with brain tumors treated with radiotherapy. The results indicated that , certain tumor types showed a prediction for overall survival and response to treatment.

The present study was a retrospective radiotherapy center-based study designed in a pioneer radiotherapy center in Western Iran, not a prospective population study. These data have provided a baseline for further larger, more detailed epidemiological studies. Our encouraging results in radiotherapy treatment of primary malignant tumors clearly highlights the benefits of definitive or postoperative radiation.

Conflict of Interest:

No conflict of interest is declared.

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