

## RESEARCH ARTICLE

# Clinicopathological Findings and Five Year Survival Rates for Patients with Central Nervous System Tumors in Yazd, Iran

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### Abstract

**Background:** The incidence rate of brain tumors has increased more than 40% in the past 20 years, especially in adults. We aimed to study the clinical and pathological findings of central nervous system (CNS) tumor patients and to evaluate their 5 year survival rates. **Materials and Methods:** The archives of all patients with CNS tumors in 6 health care centers in Yazd, Iran, from 2006 to 2013, were studied. Patients data were extracted using a checklist which included age, sex, date of reference and diagnosis, date of death, clinical signs, radiography findings, pathology report, size and location of tumor, patient treatment and grade of tumor. **Results:** A total of 306 patient records were studied in the 8 year period. The most prevalent type of tumor was astrocytoma (n=113, 36.9%). The frequency of almost all tumor types was statistically higher in male patients (p=0.025). In most cases surgery with radiotherapy was the treatment of choice (49.3%). The most frequent symptom reported was headache (in 60.8% of patients) followed by convulsions (15.7%). Most of the tumors were located in the right hemisphere (46.1%) and the frontal and parietal lobe (26% and 12%, respectively). Radiography findings displayed edema with a nonhomogeneous lesion in majority of the patients (87%). The survival fraction of the patients with malignant tumors decreased over time (0.807 in the first year and 0.358 at the end of the 5<sup>th</sup> year). **Conclusions:** Astrocytoma was the more common CNS tumor with male predominance. Overall survival rates of malignant tumors decreased over time and this was in relation with tumor grade.

**Keywords:** Survival - central nervous system - neoplasm - brain - histopathology

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### Introduction

The rise in life expectancy, improvement in healthcare along with the increase of the world's population, relative control of contagious diseases and especially the increased probability of encountering environmental risk factors have led to the rise in cancer epidemic. Cancer has an important and increasing role in the total disease load in the world (Thakkar et al., 2014). Cancer is regarded as one of the most important diseases and causes of death, after cardiovascular disease, in the 21st century (Parkin, 2001; Jemal et al., 2010). In 2008, around 12.7 million cases of cancer and 7.6 million cancer related deaths (13 percent of all deaths) were reported in the world (Jemal et al., 2011). In developed and developing countries, cancers are the second and third cause of death, respectively. According to the report from the WHO, in 15 years from now, cancer related deaths in eastern Mediterranean countries will increase by 80 to 100 percent (Omar et al., 2007). CNS tumors include a set of neoplasms which involve the brain, spinal cord or the covering membrane (meninges). Brain tumors are categorized according to their location and

histology (Mehta et al., 2011; Yilmaz et al., 2013). The brain like any other tissue of the body can bear neoplastic changes, but in the brain even benign neoplasms can cause complications as malignant tumors and this is because of the particular physiology and anatomy of the central nervous system (Sayegh et al., 2014). The incidence rate of brain tumors has increased more than 40% in the past 20 years in all age groups especially in adults (Jemal et al., 2010).

The prevalence, death rate, complications and morbidity of CNS tumors has made the precise study of this group of tumors more important. So we studied the clinicopathological findings and the five year life survival rate of patients with CNS tumors.

### Materials and Methods

#### *Study setting*

This retrospective study was conducted in Yazd, Iran. Archives of the pathology centers of 6 health care centers affiliated with Shahid Sadoughi University of Medical Sciences were reviewed. The referral centers in

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which their archives were reviewed includes: Mojibian, Goudarz, Mortaz, Rahnamoon, Shahid Sadoughi hospitals and Shahid Ramazanzade center for radiotherapy in the province of Yazd. The study was funded by Yazd University of Medical Sciences. The study protocol was approved by the institutional review board of Shahid Sadoughi University of Medical Sciences. Although the study only included a review of patients' records obtained as part of the routine medical care, patients consent forms were obtained. It is a general policy of Shahid Sadoughi affiliated health care centers to obtain a written consent form from the patients upon their freewill, agreeing that their medical records can be used for research purposes. Patients' secrecy of data was maintained and no data regarding patients' personal information was disclosed.

*Patient selection and identification*

The study population included all the patients diagnosed with cerebrospinal tumors with a confirmation from the pathology reports, who had referred to Yazd health care centers from 2006 to 2013. The inclusion criteria for entering the study was: all the patients diagnosed with cerebrospinal tumors who had a record in the pathology centers of the previously mentioned hospitals. All the records that had missing data (including test results) or a written consent form was not obtained, were excluded from the study. In result 306 records were identified and included in the study.

*Data extraction*

Patients' data were extracted using a checklist which included: age, sex, date of reference and diagnosis, date of death, clinical signs, radiography findings, pathology report, size and place of tumor, patients' treatment and grade of tumor.

Patients' demographic information including telephone number and place of residence were also extracted for further follow-ups and assessing patients' survival rates.

*Definition of variables*

The grading of the tumors was done using the fourth edition of the international classification of diseases for oncology (ICD-O), introduced by the WHO in 2007. Based on this classification tumors are classified in 4 grades ranging from grade I representing stable or slowly growing tumors to grade IV as malignant tumors. This

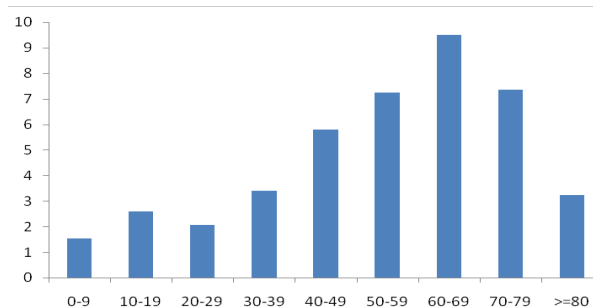
classification standard is mostly based on patients' survival rates rather than pathological findings (Louis et al., 2007).

*Statistical analysis*

The data analysis was done using the SPSS software version 11.5 for windows (SPSS Inc., Chicago, IL, USA). Patients' data were compared and analyzed using the chi-square test and for calculating the survival fraction and assessing the effect of different factors on the survival of the patients, the Kaplan-Meier and the Log rank tests were used, respectively. The descriptive data of the patients were compared using their frequency, incidence rate, mean and standard deviation. A two-tailed p-value of less than 0.05 was considered as statistically significant.

**Results**

Among the 306 cases that were studied, 161 (52.6%) were male and 145 (47.4%) were female. Patients were classified in age groups, each age group including a range of 10 years. The highest frequency distribution of cancer was in the age group of 41 to 50 years old and the lowest frequency distribution was in the 81 to 90 years old patients. This demonstrated an increase of disease incidence from 1 year old to 50 year old patients and a decrease in cancer rates after that until the age of 90. The study results show that the highest number of incidence was in 2010(54 patients). The highest age-specific incidence rate was observed from 60-69 years (9.5 per 100000 person) (Figure 1). The largest number of deaths occurred in 2011. The most prevalent type of tumor was astrocytoma (n=113, 36.9%) and then glioblastoma multiform (GBM) (24.8%) and the least frequent forms of tumor were chordoma and craniopharyngioma (both



**Figure 1. Age Specific Incidence Rate of CNS Tumors Per 100000**

**Table 1. Age and Sex Distribution for Each Tumor Type**

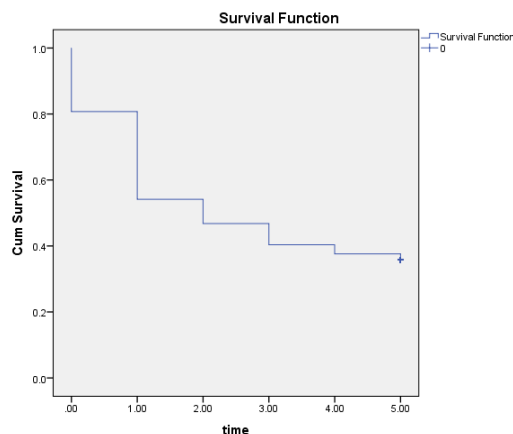
Tumor type	Total (%)	Frequency		Age (mean±SD)
		Male (%)	Female (%)	
Astrocytoma	(36.9)113	62(38.5)	51(35.1)	36.6±19.3
GBM	(24.8)76	40(24.8)	36(24.8)	46.3±19.4
Oligodendroglioma	(5.9)18	8(5)	10(6.9)	41.4±19.4
Ependymoma	(5.2)16	9(5.6)	7(4.8)	28.7±20.0
Meningioma	(16.3)50	16(9.9)	34(23.4)	51.8±14.9
Medulloblastoma	(4.6)14	10(6.2)	4(2.7)	17.6±10.1
Hemangioma	(1.3)4	4(2.5)	0(0.7)	39.8±18.3
Lymphoma	(1.6)5	4(2.5)	1(0.7)	47.0±18.7
Hemangioblastoma	(2.0)6	5(3.1)	1(0)	33.3±11.1
Craniopharyngioma	(0.7)2	2(1.2)	0(0)	13.5±7.8
Chordoma	(0.7)2	1(0.6)	1(0.7)	59.5±0.7
All	306(100)	161	145	40.6±19.9

**Table 2. Treatment Types Frequency in CNS Tumors**

Treatment	Frequency (%)
Radiotherapy	20 (6.5)
Surgery with radiotherapy	151 (49.3)
Surgery with radiotherapy and chemotherapy	95 (31)
Radiotherapy with chemotherapy	31 (10.1)
Surgery with chemotherapy	1 (0.3)
Discontinued treatment	8 (2.6)

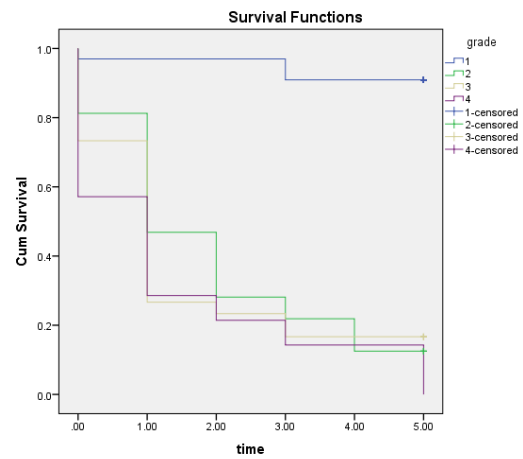
**Table 3. Radiologic (CT scan) Findings for Brain Tumors**

Tumor type	Ring-enhancing lesion		Overall	P-value
	Negative cases	Positive cases		
Astrocytoma	105(92.9)	8 (7.1)	113	P=0.252
GBM	66(86.7)	10 (13.3)	76	
Oligodendroglioma	16(82.2)	2 (11.8)	18	
Ependymoma	15(93.8)	1 (6.2)	16	
Meningioma	0 (0)	0 (0)	50	
Medulloblastoma	0 (0)	0 (0)	14	
Hemangioma	3(66.7)	1(33.3)	4	
Lymphoma	0 (0)	0 (0)	5	
Hemangioblastoma	0 (0)	0 (0)	6	
Craniopharyngioma	0 (0)	0 (0)	2	
Chordoma	0 (0)	0 (0)	2	
Overall	284(92.8)	22 (7.2)	306	



**Figure 2. Patients' Pattern of Survival During a Five Year Time Period.** Demonstrates a decrease in survival by each year, in the five year period of time. The fastest decline is seen in the first year (from 0.807 to 0.541)

0.7%). When comparing the frequency of each tumor type in the two sex groups, results show that in almost all the types of tumors the frequency was statistically higher in male patients ( $p=0.025$ ) (Table 1). Patients with Astrocytoma had a mean age of years  $36.6 \pm 19.3$  and those patients with GBM had a mean age of  $46.3 \pm 19.4$  years. The mean age showed a significant difference among the different tumor types ( $p<0.001$ ). Comparing the incidence of the tumors each year, showed that the incidence had an overall increase every year from 2006 to 2010 and then a decrease from 2010 to 2013 except for 2012. The therapy that the patients received included: radiotherapy, surgery with radiotherapy, surgery with both radiotherapy and chemotherapy or surgery with chemotherapy. In most cases surgery with radiotherapy was the treatment of choice (in 49.3% of the cases), although 8 patients did not



**Figure 3. Patients survival fraction based on the grade of the tumor.** Shows that by the increase in the grade of the tumor the survival fraction decreases and this is expected due to the fact that grading system of the WHO is mostly based on survival rates. This difference was statistically meaningful ( $p<0.001$ )

continue their therapy (Table 2). Study of patients' clinical signs included headaches, convulsion, paresis, memory and visual dysfunction and decrease in consciousness. The most frequent symptom reported was headache (in 60.8% of patients) followed by convulsion (in 15.7% of patients). Tumor types based on their anatomical position showed that the majority of the tumors were in the right hemisphere (46.1%) and in the frontal and parietal lobe (26% and 12%, respectively). Astrocytoma, GBM, Oligodendroglioma, Meningioma and Craniopharyngioma were most prevalent in the frontal lobe and Ependymoma, Hemangioma and lymphoma were most frequently seen in the spine and finally Medulloblastoma and Hemangioblastoma were mostly seen in the cerebellum ( $p<0.001$ ). Patients mostly had grade 1 and 2 tumors (both 28.8%). The radiographic findings displayed a Ring-enhancing lesion in Computed Tomography (CT) scan in 22 patients (7.2%) between the 306 total patients that were studied. These lesions were only present in Astrocytoma, GBM, Oligodendroglioma, Ependymoma, and Hemangioma. Among these tumors, GBM had the highest number of Ring-enhancing lesions (13.3%), yet none of them presented a statistically meaningful difference in this finding ( $p=0.252$ ) (Table 3). Radiography reports showed that among 76 patients whose findings were registered, 66 (87%) of them had edema with a nonhomogeneous lesion and 10 (13%) had edema with a homogeneous lesion. In the follow-up process, from the initial 306 patients only 109 patients were accessed for measuring their survival rates. The survival rates of the patients with malignant tumors decreased over time starting at 0.807 for the first year and reaching to a survival fraction of 0.358 at the end of the 5th year (Figure 2). The correlation between the tumor grade and the survival fraction was also assessed. Results showed that by the increase in tumor grade the survival fraction decreased ( $p<0.001$ ) (Figure 3).

## Discussion

The prevalence and death rates of CNS tumors

differ from one population to another depending on factors like socioeconomic variables. Countries that have better economies, have better access to advanced medical care. The prevalence of CNS tumors are less in Asian countries and this could be due to genetic and environmental factors (Zhang et al., 2014). Here, we studied the clinicopathological characteristics, incidence and survival rates of patients with CNS tumors in Yazd, Iran to obtain any relation between patients' tumor type, radiological findings, sex, age, location of tumor, and type of treatment with survival rates.

In our study the tumor frequency was higher in the male population compared to the female population and this was in coherence with other studies (Mao et al., 1991; Parkin et al., 2001; Jazayeri et al., 2013). They documented a higher frequency of cancer in the male population. Although this result was contradicted by (Porter et al., 2010; Jiang et al., 2011), which they documented higher prevalence rates in the female patients.

The lower incidence of CNS tumors in the female population has been related to factors like the protective role of the female hormones and genetic differences between males and females (Gabriella et al., 2014). Also in the recent published research article the researchers found that retinoblastoma protein (Rb), a protein known to reduce cancer risk, is significantly less active in male brain cells than in female brain cells, so males greatly susceptible to brain tumors (Sun et al., 2014).

The age of patients in the present study ranged from 1.5 years to 83 years which indicates that brain tumors can affect any person in any age, but there was a meaningful difference in the tumor frequency among the different age groups. In our study only 18.9% of the patients presented with tumors in the first two decades of their lives. The majority of our patients with CNS tumors were in a middle age group (41-50 years), and the highest age-specific incidence rate was observed from 60-69 years (9.5 per 100000 person), however in the study published by cancer incidence report of US, there was meaningful relation between the age and incidence of brain tumors, and the highest rate was reported in older men and women (80-84 years old), (SEER, 2014).

In this study the tumor incidence increased from 2006 to 2010 and after that it decreased from 2010 to 2013, except for 2012. One of the most important reasons for the sudden increase in 2012 was because of the visiting patients that referred to Yazd province from the neighboring regions. Not considering this factor is one of the problems of our study. Overlooking the ambiguous change in 2012, we could say that the tumor incidence is decreasing, which could be attributed to factors like: better early diagnostic tools, increased patient awareness, on time reference of the patients and access to improved resources. Kohler et al. (2011) studied the incidence of CNS tumors from 1975-2007, they concluded that the incidence has decreased by 1% each year and they attributed the decrease to better diagnosis, prevention and treatment. Tumor frequency was higher in the male pediatric population in the two first decades. This finding was in concordance with other studies (Ahmed et al., 2007; Mehrazin et al., 2007; Makino et al., 2010; Asirvatham et al., 2011). The main

treatment of brain tumors is radiotherapy, and this is due to different factors like the inability of chemotherapy drugs to reach the brain and the technical difficulties involving surgery (Bock et al., 2010). The treatment of choice for the majority of patients in our study was radiotherapy with surgery (for 49.3% of the patients), radiotherapy with chemotherapy (10.1%) and then radiotherapy alone (6.5%). In our study most of the tumors were malignant while Porter et al. (2010) documented a higher prevalence in benign tumors (166.5 and 158.7 per 100000 for benign and malignant, respectively). This could be attributed to the different settings in which the two studies were conducted, in which our study included patients from a hospital setting and not the general population. The most common symptoms were headaches (60.8%), convulsion (15.7%) and paresis (13.7%). Our findings were similar to Cancer Research UK (2013) study. The most common location of the brain tumors, was in the hemispheres, with frontal predominance for malignant ones. This result was in coherence with results of Pashaki et al. (2014) documented that in their study the Glioblastoma multiforme were mostly located in the frontal. The most prevalent forms of tumor, in our study, were: Astrocytoma (36.9%), GBM (24.8%) and Meningioma (16.3%). In the study reported by Manoharan et al. (2012) the most frequently tumor types were gliomas (25.4%), glioblastomas (21.5%) and astrocytomas (20.6%), that was similar to our study, despite, they didn't studied the benign tumors prevalence such as meningioma. In a systematic review by Jazayeri et al. (2013) the most common forms of tumor were Astrocytoma and Glioblastoma multiform (15.2% and 13.8%, respectively). In the study published by cancer research UK. (2013) the commonest forms were Astrocytoma (34%) followed by Meningioma (21%). However they considered Glioblastoma Multiform as an aggressive form of astrocytoma not as distinct morphological group, but we divided these two types of tumors from each other.

In present study the survival rates were decreased overtime, and also by increasing the grade of tumor the survival rates were decreased. Our findings were in line by Fuentes-Raspall et al. (2011) study, which the survival rates were decreased by tumors grade. We suggest that further studies be conducted on populations in different age groups and also controlling factors like emigration so that the results are more precise. Studies should also be designed to evaluate patients in a longer time period.

In conclusion, we conclude from our study that the incidence of CNS tumors is decreasing and among the different types of tumors Astrocytoma is the most common form. The tumor frequency rate is higher in the male population compared to the female population and the incidence rate was highest in older age group (60-69 years old). We also conclude that the most common symptom is headache, the majority of CNS tumor patients have grade 2 and 3 tumors and they mostly present edema with a nonhomogeneous lesion in their radiography findings. Overall survival rates were decreased overtime and this was in relation with tumor grade.



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