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Research Article

Primary Malignant Brain Tumor Trends in Southern Iran, 2001-2017: An Alarming increase in Glioblastoma

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Abstract

Introduction

Primary Brain tumors which include a 1.7 percent of all cancers among which glioblastomas are the most lethal and the most frequent malignant types. Ionizing radiation and some genetic factors have been reported as the etiology of such cancers. We are reporting the trends in the Brain tumors with a focus on malignant types and its outcome in the South of the Iran for the first time.

Methods

We selected all the patients with primary brain tumors who undergone brain surgery at teaching hospitals the

Shiraz Medical School between 2001 and 2017. Data was obtained from Fars Population-based Cancer Registry. ICD-O-3 morphology coding system according to WHO 2007 classification of CNS tumors was used for grouping the tumors. Using SPSS, Total Growth Rate (TGR) and Incidence Rate (IR) were calculated to assess the changes overtime.

Results

A total number of 2130 (male: 890, 41.8% and female: 1240, 58.2%) brain tumor cases from 2001 to 2017 were included in this study. The highest Incidence Rate (IR) was found in 'unspecified tumors of the brain' (2.74 per 100000) between 2011 and 2015 followed by 'Astrocytoma' (1.34 per 100000) between 2006 and 2010) and 'Glioblastoma' (1.25 per 100000) between years 2011 and 2016. Additionally, the Glioblastoma showed the highest IR in those aged between 30 and 59 of years (0.42 per 100000).

Conclusion

An upward trend in the rate of malignant brain tumors in the Fars province could be an alarm sign for more studies to be done especially from the etiology point of view.

Key words: Primary brain tumor; Malignant; Incidence rate; Trend; Glioma

1. Introduction

Primary Brain tumors which include a 1.7 percent of all cancers [1] are a heterogeneous group of diseases that their entity could be categorized based on the biological behavior, histopathological pattern as well as morphology, anatomical location and age [2,3]. Although the precise etiology of brain tumors have not been identified yet, several studies have reported risk factors such as Ionizing radiation and some genetic factors for both benign and malignant brain neoplasms [4-6]. The clinical manifestations of such tumor usually originates from the anatomic location of the tumor and the part of the brain which is involved, however, the tumor most prevalent clinical presentation include seizure, headache, fatigue and cognitive dysfunction [7]. Based on tumor type and anatomical location, malignancy potential, and the patient's age, treatment strategy could be different for each patients and usually includes a combination of surgery in addition to radiotherapy, and chemotherapy. Additionally, imaging has been always the most common method for diagnosis if such tumors [7,8]. From the prevalence point of view, among these intracranial tumors, Meningiomas, representing 36 percent of all, are the most frequent type. On the other hand, Gliomas are the most frequent malignant type which consist of 75 percent of cases presenting with malignant brain tumors [1]. Several studies have reported the trend of the intracranial tumors in different countries (9-17). The incidence rate of tumors are controversial especially regarding malignant tumors. Most of these studies have reported an increase in the incidence of malignant and non-malignant brain tumors in elderly and also adolescents [11,14]. However there are reports from some countries which did not showed any overall increase trend in incidence of malignant tumors [13]. Some studies have reported a plateaued or even decreasing trend in the incidence of the CNS tumors in general [18]. On the other hand, some of these papers have reported difference between incidence of CNS tumors in males and females [15].

In Iran, Araghi et al have reported an increase trend of brain and CNS tumors for all ages in Golestan Province located in the South East littoral of the Caspian Sea in Northern Iran. They have also reported a higher incidence rate in men than in women [9]. In

this current study, we are reporting the trends in the Brain tumor and its outcome in the South and Southwest of the Iran for the first time.

2. Methods

2.1 Data resources

The current data is collected from Cancer registry center (CRC) belonging to Shiraz University of Medical Sciences which was established in (1995). Fars province is located in the southwest of the Iran and its capital is Shiraz city. This province has a population of 4.85 million according to the latest census in 2016 representing about six percent of total Iranian population.. Shiraz University of Medical Sciences, one the oldest medical schools nationwide, has four main general teaching hospitals (Namazi, Chamran, Rajae and Sa'di) and have been hosting patients from the most of the south and west part of the Iran. For current study, we selected all the patients with primary brain tumors who undergone brain surgery from 2001 to 2017. Demographic data of patients including gender, age at diagnosis, calendar year of diagnosis and history of previous malignancy were obtained. Tumor characteristics including tumor location, type and tumor size were also considered. ICD-O-3 morphology coding system according to WHO 2007 classification of CNS tumors was used for grouping the tumors (Table 1) [13]. The primary malignant barin tumors (ICD-O-3 morphology codes 9380–9451) and other unspecified primary brain tumors (ICD-O-3 morphology code 8000) were included. Additionally, based on data on cancer registery form the tumor location was reclassified according to ICD-O-3.

Glioma subtype	Morphology code
Astrocytic tumors	
Astrocytoma	9400, 9411, 9420
Anaplastic astrocytoma	9401
Glioblastoma	9440–9442
Oligodendroglial tumors	
Oligodendroglioma	9450
Anaplastic oligodendroglioma	9451
Oligoastrocytic tumors	
Oligoastrocytoma grade II and III	9382
Ependymal tumors	
Ependymoma	9391, 9393
Anaplastic ependymoma	9392
Unspecified malignant glioma	9380
Other malignant tumors	
Other specified tumors of the brain	9381, 9390, 9424, 9430, 9470,
Unspecified tumors of the brain	8000

Table 1: malignant primary brain tumors based on ICD-O-3

All the patients who have undergone surgery for brain tumor and their data were registered in Tumor Registry Center got involved in this study. There was no age or sex limitation. The patients whom their birth place were out of Fars provenance or where living out of this provenance were excluded. All the patient who had a second surgery due to recurrence were also excluded. Incidence rate was calculated with 95% confidence intervals (CI) for all tumors divided based on age group, histological type, year of diagnosis and gender. The average annual percent change (APC) was estimated using the following formula: (Numbers at 2016- Numbers at the first year of diagnosis)/(Numbers at the first year of diagnosis*duration). All the calculation were performed in SPSS Version 21.0.

3. Results

A total number of 2130 (male: 890, 41.8% and female: 1240, 58.2%) brain tumors were reported to the FPCR during 2001 to 2017. Divided by the age-groups, in total, the number of the cases were mostly aged between 50-60 (n=390, 18.3 %) followed by 30-40 years old (n=328, 15.4%). Additionally, the number of cases in those between 20-30 years of age was less than in other age groups (Table 2).

Variable	Subgroup	Frequency	
		Number	%
Gender	Female	890	41.8
	Male	1240	58.2
Age Group	<20	267	12.5
	20-30	237	11.1
	30-40	328	15.4
	40-50	320	15
	50-60	390	18.3
	60-70	301	14.1
	>70	287	13.5

Table 2: The frequency of malignant brain tumors based on gender and age groups

The Total Growth Rate (TGR) of the tumors in males and females was almost equal (62 and 61.5 % respectively). However, this growth in various subgroups was quite different. TGR showed a 160 % increase in those older than 70 years old followed by 100 % increase in those younger than 20 years old. The least increase was also in those with 20-30 years old of age (5.6%) (Table 3).

Variable	Subgroup	Total growth rate (%)
Gender	Female	61.5
	Male	62
Age Group	<20	100
	20-30	5.6
	30-40	43.3

	40-50	48.9
	50-60	36.7
	60-70	38.7
	>70	160

Table 3: The TGR of malignant brain tumors based on gender and age groups

Among all the tumor types diagnosed based on the histopathological features, the maximum TGR was found in Glioblastoma (+360 %) followed by Anaplastic Astrocytoma (+33.3 %). However, those categorized as 'Unspecified tumors of the braain' showed a +323.2 % of TGR. On the other hand, Ependymoma showed a 0 % of TGR. Additionally, the overall TGR of the brain tumors was found as +61.8 5 during these years (Table 4). Additionally, figure 1 shows the trend of various types of malignant brain tumors based on the number of the patients between years 2001 to 2016.

Tumor	Subgroup	Frequency		Total growth rate (%)
		Number	%	
Astrocytic tumors	Astrocytoma	505	23.7	12.7
	Anaplastic astrocytoma	128	6	33.3
	Glioblastoma	388	18.2	306.7
Oligodendroglial tumors	Oligodendroglioma	81	3.8	28.6
	Anaplastic oligodendroglioma	57	2.7	27.3
Oligoastrocytic tumors	Oligoastrocytoma grade II and III	34	1.6	7.7
Ependymal tumors	Ependymoma	51	2.4	0
	Anaplastic ependymoma	9	0.4	25
Unspecified malignant glioma		46	2.2	2.2
Other malignant tumors	Other specified tumors of the brain	210	9.9	12.4
	Unspecified tumors of the brain	621	29.2	323.2
Total		2130	100	61.8

Table 4: The TGR of various kind of brain tumors.

For the five most important tumors of the brain from this study's point of view, the trend is shown in the figure 1. Almost all the tumors showed an increase trend from 2001 to 2010 and after that, stabilized. However an outbreak in the number of the unspecified tumors of the brain was found from 2012 to 2016.

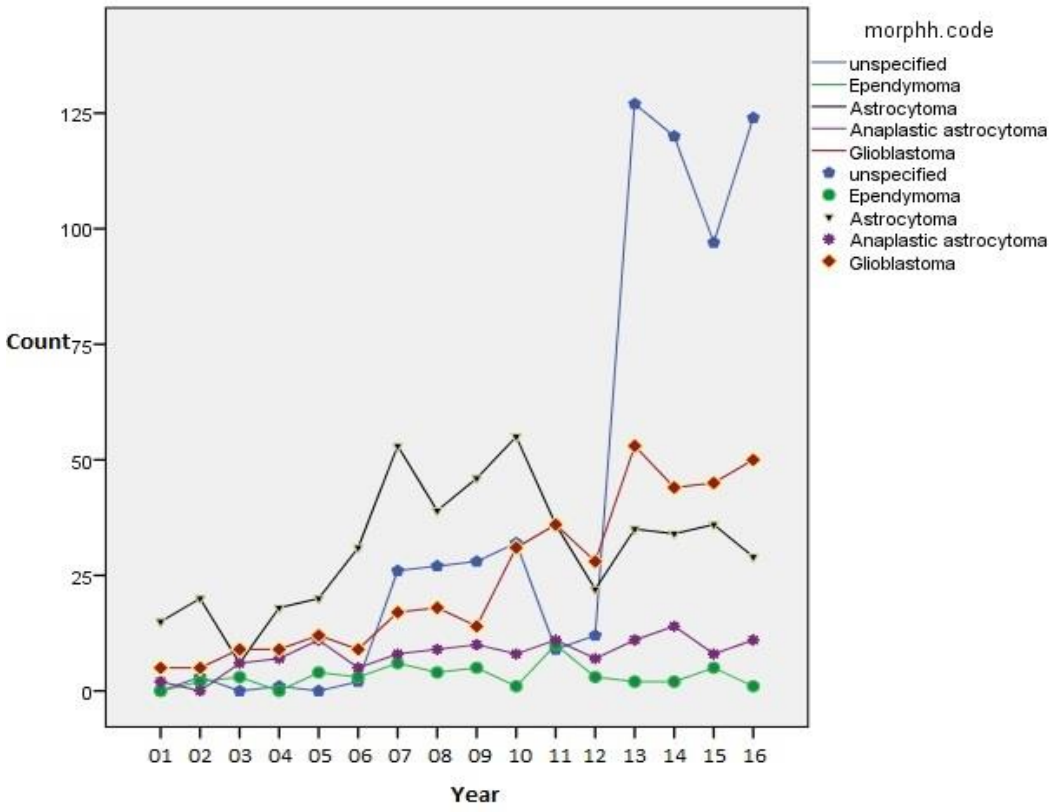

Figure 1: Trends of the tumors of the brain based on the number of the each tumor from 2001 to 2016.

In term of anatomical location of the tumors, the most prevalent location of malignant brain tumors was reported as unspecified, these consist of cases that the exact tumor location was not mentioned (n=1198, 56.2%). However, in those which location was exactly reported, the most prevalent one was the frontal lobe (n=275, 12.9%) followed by the parietal lobe (n=208, 9.8%). Interestingly, although the number of the malignant neoplasms of the 'overlapping sites of the brain' was not quite a lot, the TGR of the tumors in this group was the highest among the various tumors anatomical locations (Table 5).

Anatomical location	Frequency		Numbers at the first year of diagnosis	Numbers in 2016	Total growth rate (%)
	Number	%			
C71.0	27	1.3	1	3	16.7
C71.1	275	12.9	4	27	38.3
C71.2	208	9.8	2	13	36.7
C71.3	100	4.7	1	5	30.8
C71.4	43	2	1	4	27.3
C71.5	29	1.4	1	2	7.7
C71.6	107	5	5	13	10.7
C71.7	22	1	1	3	13.3

C71.8	121	5.7	1	18	113.3
C71.9	1198	56.2	9	138	95.6
Total	2130	100	22	226	61.8

Table 5: Frequency and TGR of the malignant brain tumors categorized based on their anatomical location (C71.0: malignant neoplasm of cerebrum, except lobes and ventricles, C71.1: malignant neoplasm of frontal lobe, C71.2: malignant neoplasm of temporal lobe, C71.3: malignant neoplasm of parietal lobe, C71.4: malignant neoplasm of occipital lobe, C71.5: malignant neoplasm of cerebral ventricle, C71.6: malignant neoplasm of cerebellum, C71.7: malignant neoplasm of brain stem, C71.8: malignant neoplasm of overlapping sites of brain, C71.9: malignant neoplasm of brain unspecified).

The Incidence Rate (IR) per 100,000 population of various brain tumors is represented in Table 6. The highest IR was found in 'unspecified tumors of the brain' (2.74 per 100000) between 2011 and 2015 followed by 'Astrocytoma' (1.34 per 100000) between 2006 and 2010) and 'Glioblastoma' (1.25 per 100000) between years 2011 and 2016.

Tumor	Subgroup	Time period		
		2001-2005	2006-2010	2011-2016
Astrocytic tumors	Astrocytoma	0.66	1.34	0.89
	Anaplastic astrocytoma	0.18	0.27	0.29
	Glioblastoma	0.29	0.68	1.25
Oligodendroglial tumors	Oligodendroglioma	0.09	0.19	0.18
	Anaplastic oligodendroglioma	0.01	0.09	0.21
Oligoastrocytic tumors	Oligoastrocytoma grade II and III	0.01	0.01	0.16
Ependymal tumors	Ependymoma	0.07	0.15	0.07
	Anaplastic ependymoma	0.006	0.02	0.01
Unspecified malignant glioma		0	0.05	0.21
Other malignant tumors	Other specified tumors of the brain	0.27	0.23	0.31
	Unspecified tumors of the brain	0.03	0.71	2.74

Table 6: The Incidence Rate of various brain tumors in different time periods.

The IR of the five most important primary brain tumor from the perspective of our study was calculated for different age groups in the entire sixteen years of the study which is reported in the Table 7. In this regard, the highest IR was found in 'Unspecified malignant glioma' (0.55) in those aged more than sixty years old followed by Astrocytoma in those aged 3-59 years (0.52). Additionally, the Glioblastoma showed the highest IR in those aged between 30 and 59 of years (0.42). (Figure 2)

Tumor	Subgroup	Age groups		
		<30 yrs	30-59 yrs	>60 yrs
Astrocytic tumors	Astrocytoma	0.31	0.52	0.12
	Anaplastic astrocytoma	0.04	0.17	0.03
	Glioblastoma	0.11	0.42	0.21
Ependymal tumors	Ependymoma	0.05	0.02	0.01
Unspecified malignant glioma		0.14	0.48	0.55

Table 7: The IR of the five most important brain tumors from the perspective of this study in different age groups for the entire 16 years.

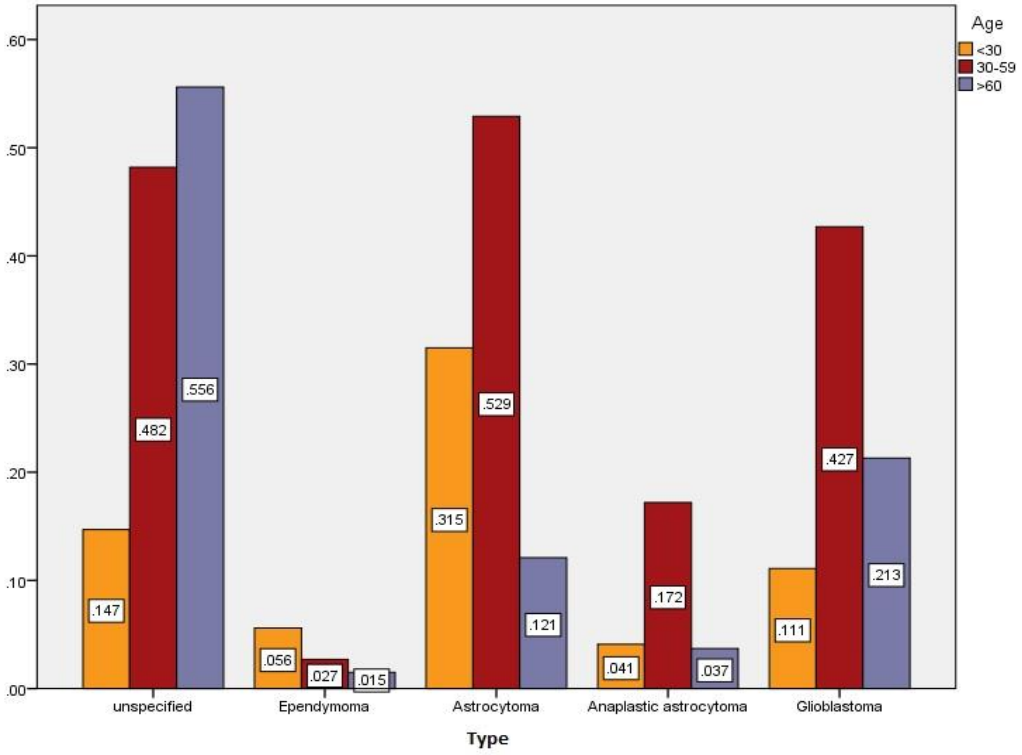

Figure 2: The incidence rate of five different tumors based on age groups.

3. Discussion

In this descriptive study, we found an upward trend in the rate of malignant brain tumors in the Fars province which is located in south part of Iran between 2001 and 2016. The most common types of such tumors were unspecified glioma, Astrocytoma and Glioblastoma. This finding is compatible with the previous reports in Iran [19,20]. In term of incidence rate trend, Araghi et al have reported a stabilization in the trends after 2008 [9]; in our study in the most subgroups based on the histopathological features, it shows such a stabilization. However, an upward trend was found in malignant subgroups such as Glioblastoma and anaplastic astrocytoma. Yet, the difference between our study and Araghi et al. study is the duration of our study. They reported data from

2004 to 2013 while we are reporting data from 2001 to 2016 which may affect the reliability of our data. However, the geographical location for the studies has also been reported as an important factor in recent studies both from Iran and worldwide [21] which could affect the result of each study. Besides, an important result of our study showed a dramatic increase in the TGR of malignant brain tumors in age group less than 20 years (a 100% increase in TGR), in addition to a considerable increase in TGR of Glioblastoma which showed a +306.7 percent increase during these years. Additionally, in those aged between 30 and 59 years of age, the IR of the most important primary malignant brain tumors showed the highest level which is not reported before in Iran. On the other hand, in a recent study published by Salimi et al in 2020, they also have reported an increasing trend of overall CNS tumors [21]. However they have reported of all kind of the CNS tumors while we are reporting of just the malignant brain tumors. The stabilization in the incidence trend of malignant tumors are reported in different studies in Europe, although they reported an increase in incidence rate of overall benign tumors but malignant glioma of brain remained in a plateau [13,23]. Such important results need to be accurately followed in the future to fully understand whether an outbreak of malignant brain tumors is happening in special group of people in the Iranian society or not. There are several reports of trends in brain tumors incidence worldwide both in adults and children [10, 11, 13-17, 22, 23]. Some of these studies have reported a stable increase rate with no departure from linearity [13]. On the other hand, some has reported an increase in annual incidence rate of benign tumors only and has reported the malignant ones stable [23]. In our study, we found a quite upward trend in malignant brain tumors incidence rate such as Glioblastoma, Oligodendroglioma, Astrocytoma (2001 to 2010) and a stability in some other tumors such as Ependymoma. On the other hand, the same study [13] has reported an increase in only those older than 80 years of age. While in our study, we found the highest incidence rate in those aged between 30 to 59 years. In term of TGR, on the other hand, almost all the age groups showed an increase during the entire sixteen years of which the least TGR was found in those with 20 to 30 years of age. Additionally, there are reports consistent with our findings regarding an increase in the burden of primary CNS tumors for a period of 60 years but a steady rate of that from early 2010 [14]. Although we are reporting the primary malignant brain tumors only, while they have reported the overall CNS tumors and also benign brain tumors such as meningioma. Regarding the reason why such increase in trends and incidence rates of the tumors have occurred, some research suggest the advances in diagnosis and risk factor augmentation [15, 21]. We believe that since at least 20 years ago, Computed Tomography which is quite capable of diagnosing brain tumors has been always available at our center, Shiraz University of Medical Sciences as the referral center for the southwest part of the Iran; so, that could not be the reason underlying the upward trend of such tumors. On the other hand, risk factor which have been suggested as the underlying etiology of these tumors such as environmental factors including radiation, in addition to genetics, would be the main reason which needs more investigation as more studies are reporting the importance of the genetic factors related to the incidence of the brain tumors [4, 24-26]. It is important to be mentioned that, in this study we have reported the malignant brain tumors only and we have investigate the incidence rate and trend of such tumors. Investigating all the brain tumors including benign ones such as meningioma and also all the brain tumors such as metastatic in addition to primary ones may lead

to a report different from what we are reporting which of course need of such an investigation is sensible. What we are reporting, is showing an alarm and bringing up a serious question whether an outbreak in malignant brain tumors especially glioblastoma as the most lethal one is happening or not? Additionally there are reports and evidence that non-ionizing radiofrequency radiation could lead to brain tumors such as Schwannomas and malignant gliomas [27, 28]. Recently the exposure to this type of radiation has increased considering the more use of mobile phones and expansion of telecommunication towers. Also the radiofrequency radiation used to noise in TV networks should not also be forgotten. So the question is, acting as a radiofrequency non-ionizing radiation, and based on the amount of the radiation applied, could it such these noises applied to International TY networks, be a possible reason for such an increase in the brain tumors in Fars province of Iran? Another important factor is the regional environmental changes that have affected the climate in southern Iran and Iraq such as air prolusion, warming and increased use of toxins in food industry. Answering such questions needs further investigation on malignant brain tumor trends in other provenance of Iran and also in neighboring contraries. Also access to the accurate information regarding the level of these radiofrequency noises can be helpful.

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