

## RESEARCH ARTICLE

# Glioma Epidemiology in the Central Tunisian Population: 1993-2012

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### Abstract

**Background:** Glioma is a heterogeneous central nervous system (CNS) tumor group that encompasses different histological subtypes with high variability in prognosis. The lesions account for almost 80% of primary malignant brain tumors. The aim of this study is to extend our understanding of the glioma epidemiology in the central Tunisian region. **Materials and Methods:** We analyzed 393 gliomas recorded in cancer registry of central Tunisia from 1993 to 2012. Crude incidence rates (CR) and world age-standardized rates (ASR) were estimated using annual population data size and age structure. Statistic correlations were established using Chi-square and Kaplan-Meier test. **Results:** Tunisian glioma patients were identified with a mean age at diagnosis of 48 years and 1.5 sex ratio (male/female). During the 19 years period of study the highest incidence value was observed in male group between 1998 and 2002 (CR: 0.28, ASR: 0.3). Incidence results underline increasing high grade glioma occurring in the adulthood in the last period (2007-2012). Median survival was 27 months, with 1-, 2- and 5-year survival rates of 42%, 30% and 26%, respectively. Survival was greater in patients with younger age, lower tumor grade, infratentorial tumor location and undergoing a palliative treatment. **Conclusions:** This central Tunisia gliomas registry study provides important information that could improve glioma management and healthcare practice.

**Keywords:** Glioma - epidemiology - incidence - Tunisia - trends

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### Introduction

Gliomas are primary CNS tumors with glial cell origin. The international classification of glioma (International Classification of Diseases for oncology: ICD-O-3) is based on the stem cell type that the tumor originates from (astrocytic or oligodendroglial) (Louis et al., 2001). They are also subdivided according to their degree of malignancy into low or high grade gliomas (Louis et al., 2007).

The incidence of astrocytic tumors has been estimated at 4.8 (3.0 high grade, 1.2 low grade and 0.6 glioma NOS) per 100,000 per year in Europe followed by oligodendroglial tumours (0.4 overall; 0.3 low and 0.1 high grade) (Crocetti et al., 2012). Lower incidence was reported in the developing countries (Ohgaki and Kleihues, 2005).

Over the last years epidemiological investigations of CNS tumors and Glioma specifically led to collect many worldwide data and made it to the reach of all. The purpose of such investigations was to characterize glioma dissemination in numerous countries.

As a result, these studies have been considered one of the cornerstones that have participated into glioma healthcare advances. These findings have contributed to glioma better understanding and therapeutic strategy improvement, in developed countries.

In Tunisia, despite of the advances in gliomas' management, little is known about their epidemiology. This makes characterizing Tunisian glioma epidemiology a challenge for us. In the future, our study could provide a public health progress, particularly in early diagnosis and successful therapy of Tunisian gliomas.

In order to review the epidemiological features of gliomas in Tunisia, we carried out a retrospective study on 393 glioma cases recorded in the cancer registry of the centre located at the Farhat Hached university hospital, of Sousse, Tunisia, for the period of 19-years (1993-2012).

### Materials and Methods

#### *Data collection and follow-up*

From 1993 to 2012, we included in our study all patients diagnosed with a glial tumor originated from

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central Tunisian population, and who were recorded in the central Tunisian cancer registry. The local ethics committee has approved this study

Our studied cohort is composed by 393 patients originated from a region covering six provinces: Sousse, Monastir, Mahdia, Kasserine, Sidi Bouzid and Kairouan. The report of population composition arranged by age group and sex during the period of 19 years (1993-2012) was provided by The NIS (National Institute of Statistic). Today, according the NIS reports the central Tunisian population represents 23% of overall Tunisia population (641.700 million inhabitants). This population is mainly composed by young inhabitants (37.4% less than 20 years old) (Missaoui et al., 2010).

*Statistical analysis*

The studied cohort characteristics were evaluated including patient’s age and gender. Tumor Data included: location, size, histology subtypes and grade. This study also focused on patient follow up and therapeutic strategy: surgical resection and/ or palliative treatment. Patients with missing data were excluded from the statistic analysis.

We evaluated the glioma incidence by dividing calendar-years into 4 periods of four successive years (1993-1997, 1998-2002, 2003-2007, and 2008-2012). The CR (Crude ratio) during the whole 19-years period was calculated in each year for women and male separately. Similarly the ASR (Age standardised incidence rates per 100,000) were computed in each age group using the world standard population.

Survival analysis was performed though SPSS 10.0 software. A p value of less than 0.05 was considered as

significant. Correlations were assessed by Chi-square analysis. The overall survival was assessed using Kaplan-Meier analysis.

**Results**

*Glioma incidence*

We included in our analysis glioma cases diagnosed between 1993 and 2012. The CRs and ASRs are shown in Table 1. Increasing values of CR as well as ASR were observed, with a highest estimated value observed in man during the period of 1998-2002 (CR: 0.28, ASR: 0.3).

*Patients’ gender and age distribution*

During the period of study, 393 gliomas were listed, including 60 % of male and 40 % of female with a 1.5 sex ratio (male/female). The median age at diagnosis was 48 years ranging from 2 to 90 years. Our patients’ age was distributed into 4 groups: old adult, adults, young adults and paediatric (Table 2). Adult (>40 years old) and young adult (>15 and <40 years old) frequencies were 0.6 and 0.27 respectively. Meanwhile paediatric tumors were less diagnosed with a frequency of 0.1.

*Tumor size location and histology subtypes*

Tumors occur in the supratentorial location in 179 of cases. The predominant Tumor location was frontal (freq=0.3). The parietal and temporal locations were equally distributed with a frequency of 0.25. Juxta-Ventricular location was noticed in only 12 cases (freq=0.04). 111 tumors were located in the infratentorial region including: 23 occipital (freq=0.08), 18 cerebellar (freq=0.06) and 5 brain stem cases (freq=0.02).

**Table 1. Incidence and Age-standardized Rates (per 100,000) of Glioma in Men and Females, 1993-2012**

Calendar Periods	No age group			Difference Adult vs pead	No High grade	No Low grade	No Women	No Men	CR women	CR Men	ASR Women	ASR Men
	0-15	15-40	>40									
1993-1997	1	7	21	20	23	5	12	17	0.05	0.07	0.06	0.09
1998-2002	13	20	65	52	75	22	36	61	0.13	0.24	0.17	0.3
2003-2007	14	26	63	49	74	32	59	48	0.2	0.21	0.23	0.19
2008-2012	9	43	93	84	59	44	26	55	0.08	0.18	0.09	0.18

\*Footnotes: No , new cases registered ; ASR, age-standardized rates; CR, crude incidence rates.

**Table 2. Survival Analysis, Mean Overall Survival Rate, 1-, 2- and 5-year Relative Survival (%) and p value of Kaplan Meier Test**

		Frequencies	Survival analysis					p value
			Mean survival (months)	IC 95%	1 year	2 years	5 years	
Gender	Men	0.6	6	3.3-6.8	45	31	25	0.81
	Women	0.4	6	5.4-6.5	38	28	26	
Age	Paediatric (< 15 years )	0.1	36	/	60	53	46	0.001*
	Young adult ( 15-40 years )	0.27	12	2.3-21.6	57	44	36	
	Adult ( 40-70 years )	0.6	6	5.5-5.4	46	23	21	
	Old adult (+70 years)	0.3	3	0-6.3	8	8	0	
T.size	<5 cm	0.53	18	9.06-26.09	67	46	39	0.96
	>5 cm	0.46	18	9.6-26.3	58	37	37	
Location	Supratentorial	0.62	6	5.4-6.5	34	21	17	0.007*
	Infratentorial	0.38	8	5.2-10.7	44	40	36	
Grade	Low grade	0.3	36	/	22	20	17	0.00*
	High grade	0.7	6	6.5-6.4	19	12	10	
Treatment	Surgery	0.7	6	5.6-6.3	45	32	27	0.004*
	Surgery+palliative	0.3	18	6.8-29.1	62	46	42	

\*95% CI: 95% confidence interval. \*Significant trends (p<0.05)

The median tumor size was 4 cm. Measurement was ranked according an ascending scale with 1 cm of tumor size. 37% of tumors measured more than 5 cm, 49% between 4.9 and 2 cm and 13% were less than 1.9 cm (Table 2).

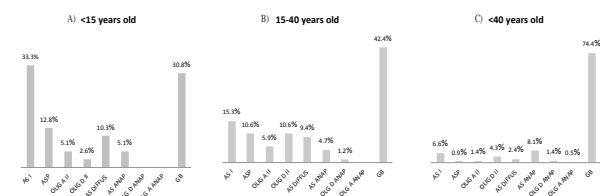
All resected tumors were microscopically analysed in duplicate. Gliomas cohort frequencies was composed by: 0.12 astrocytomas, 0.05 pilocytic astrocytoma, 0.07 diffuse astrocytoma, 0.02 oligodendrogliomas, 0.06 oligoastrocytomas, 0.05 anaplastic astrocytoma, 0.015 anaplastic oligodendrogliomas, 0.01 anaplastic oligoastrocytomas and 0.6 Glioblastoma.

#### Tumor histological subtypes distribution and correlation with age and location

Glioblastoma consists of the most common histological subtype. It was mainly observed among adults group (freq= 0.74). Meanwhile astrocytoma grade I and Pilocytic astrocytoma group occurred most frequently in the paediatric group ( freq=0.33 and 0.13). However, in the adult group astrocytoma grade I frequency was closer to the anaplastic astrocytoma (freq=0.08). Diffuse astrocytoma kept approximatively similar frequencies in both adult and paediatric group: 0.09, 0.1 respectively. Oligodendroglial tumors seem to be rare with a maximum frequency of 0.11 among young adults. Oligoastrocytoma were rare in the adult group but present in paediatric and young adult group (freq=0.05, 0.06). However anaplastic oligoastrocytoma were only present in the adult group at a very low frequency. Pilocytic astrocytoma has an unexpected high frequency of 0.11 in the young adult group with a predominant rate noticed in the paediatric group (0.013). Interestingly, 2 pilocytic astrocytoma cases were noticed among adults( Figure 1).

Our studied cohort was mainly composed by high grade tumors (70%). Only 30% represent the low grade group.

Table cross analysis using Chi-square test between tumor grades and patients' age groups demonstrated a significant association. Thus, high grade tumors were found to be more frequent in supratentorial location (rate =0.4). However low grade gliomas mostly occur in infratentorial locations (rate= 0.2). Similarly, tumor grade and location association was further assessed using Statistic Chi-square correlation that showed a significant p value (p=0.00).



**Figure 1. Pourcentage Distribution of the Various Histological Types of Tumours in Paediatric (a), Young Adult (b) and Adult Group (c).** AS I: astrocytoma grade I, ASP: pilocytic astrocytoma, OLIG A II: oligoastrocytoma, OLIG D II: oligodendroglioma, AS Diffus: diffus astrocytoma grade II, AS ANAP: anaplastic astrocytoma grade III, OLIG A ANAP: oligoastrocytoma grade III, OLIG D ANAP: oligodendroglioma grade III, GB: glioblastoma

#### Survival correlations

Survival data were available for only 171 patients. Those cases demonstrated 1-, 2-, and 5-year overall survival rates of 42%, 30% and 26% respectively, with a mean overall survival of 27 months.

#### Survival analysis of patient gender

Both cohorts of men and women patients had a median survival of 6 months. No significant overall survival difference was detected between the 2 genders (Figure 2.b).

#### Survival analysis correlation between patients' age and tumor location

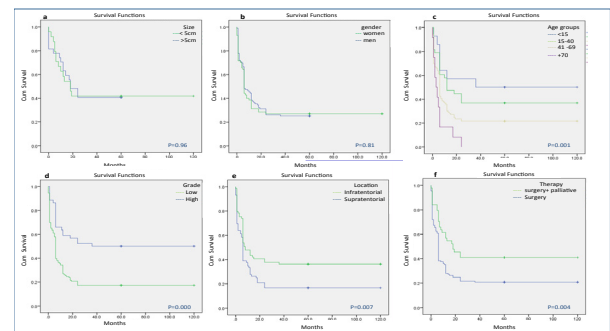
Age group analysis showed that median survivals for paediatric, young adult and adult patients were 36, 12 and 6 months, respectively. The lowest mean survival rate was found into more than 70 years old patients (3 months only) (Table 2). Kaplan Meier test revealed a significant statistic survival difference between the 4 groups (p=0.001) (Figure 2c).

Kaplan Meier test analysis also identified significant difference in overall survival between tumor location (p=0.07). Supratentorial tumors showed a lower median survival (6 months) than the infratentorial (8 months) (Figure 2e).

#### Survival analysis correlation between tumor grade (low/high) and treatment strategy

Low grade tumors showed a median survival of 36 months, while high grade tumors showed a median survival of 6 months only. High grade cases demonstrated 1, 2, and 5 year survival rates of 19%, 12%, and 10%, respectively. In low grade glioma, Survival was slightly better with 1, 2, and 5 year survival respective rate of 22%, 20% and 17% (Table 2). Survival difference between low and high grade groups was found to be significant using Kaplan Meier test (p=0.00) (Figure 2d).

Interestingly, we noticed markedly prolonged survival (median= 18 months) in patients receiving surgical resection associated with palliative treatment (radiation and/or chemotherapy). Patients undergoing only tumor resection presented median overall survival of only 6 months. Depending on therapeutic strategy statistic significant difference was found (p=0.04) (Figure 2f).



**Figure 2. Kaplan-Meier Survival Plots of the Entire Glioma Cohort Stratified by A) Tumor size; B) Patient gender; C) Patient age; D) Tumor grade; E) Tumor location and F) therapeutic strategy**

## Discussion

Brain tumors are relatively rare events. The incidence of gliomas has increased worldwide since the late 1970 (Larjavaara et al., 2007). The term 'glioma' encompasses all tumors that are thought to be of glial cell origin. Gliomas account for almost 80% of primary malignant brain tumors (Schwartzbaum et al., 2006).

The World Health Organization classifies gliomas into astrocytic tumors (A), oligodendroglial tumors (OD), glioblastoma (GB) and mixed gliomas: oligoastrocytic (OA) (Davis et al., 2008). According to their degree of malignancy, glial tumors are classified into 4 grades. Grade I or II tumors are termed low-grade Gliomas (Louis et al., 2001). The term malignant or high-grade glioma refers to tumors that are classified as: Grade III (anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AOD). The Highest grade gliomas subtype is grade IV encompassing Glioblastoma (GB) (Louis et al., 2007).

We report here a retrospective study of a large cohort of gliomas from central Tunisian population. Our studied cohort included 393 gliomas diagnosed between 1993 and 2012. We found that the ASR of gliomas in the last 5 years (2007-20012) was 0.18 per 100.000 people. Tunisian glioma seems to be slightly more common in men than in women. The male to female crude rates ratio was estimate about 1.5 in Tunisia.

In previous study, the Central nervous system tumor incidence is higher among male than female (M/F=1.4) (Jazayeri et al., 2013). Similarly, in glial tumor the male to female crude rates ratio is ranged between 1.4 for astrocytic tumors and to 1.3 for the oligodendroglial (Crocetti et al., 2012)

In European population, there are about 26,610 new diagnosed glial tumors per year during 1995-2002. The ASR for glial tumours overall was reported about 11.9 per 100.000 person per year (Crocetti et al., 2012). In western Country the ASR was 3.9 for male and 2.4 for female per 100.00 (Manoharan et al., 2012).

Meanwhile, the highest ASR rate in central Tunisia was found in the period of 2003-2007 with 0.19 in men and 0.23 in women. This may be explained by a better access to neurosurgical services, improvement and availability of magnetic resonance imaging (MRI) since 2006; beginning of MRI technology in central Tunisia.

The highest frequency of glioma was found in adult group. Comparing with other countries, Tunisian Glioma median age at diagnosis (48 years) was relatively younger. Indeed, in the United States the median age estimated at diagnosis for glial tumours is 59 years (Hess et al., 2004) (Crocetti et al., 2012). However including all primary intracranial tumor, Iranian study reported a median age of 34 years (Mehrazin et al., 2006).

Besides, we found that the incidence rates difference between adult and paediatric groups increased during the last 5 years. Thus, latterly gliomas seem to occur more frequently in older ages. Specifically a significance increase of high grade glioma was described (Barchana et al., 2012). Similarly, American study assessment described an increase of incidence rate with the 4th power of age in glioblastoma subtype (Dubrow and Darefsky, 2011).

In our case, this could be explained by a slight variability in the age ranges of Tunisian population. It also may be due to increasing frequency of high grade glioma mostly adult tumors. Although, glioma incidence increases with age, some subtypes remain more common in younger adults.

Previous study showed that age gradient was in proportion with tumor grade (Bhurgri et al., 2011). Our current statistic correlation demonstrated a strong association between high grade gliomas and adult age group (>40). Likewise, low grade gliomas were correlated with paediatric and young adult group (<40).

As regard to tumor location, high grade gliomas mostly occur in supratentorial location whereas the low grade tumors seem to be more frequent in infratentorial region. This could be explained by the high frequency of frontal Glioblastomas.

On focus on survival analysis, mean Tunisian glioma overall survival was 27 months with 1-, 2-, and 5-year overall survival rates of 42%, 30% and 26% respectively. In Europe (1995-2002) one- and five year glial tumors survival were respectively 56.9% and 19.6% (Crocetti et al., 2012).

Non significant survival difference was found between genders in our studied cohort. By contrast, overall survival after cancer diagnosis was slightly higher for European women than for men (Micheli et al., 2009).

Recent study proved that, five-year survival with glial tumours was also higher for women (20.7%) than for men (18.7%) (Crocetti et al., 2012).

We noticed that, better survival was in paediatric patients and lower in the adults group. Survival rates in the group of older patients with more than 70 years old remain disappointingly low, despite decades of advances in surgery, radiation, and chemical therapies. In the same way, on the same European study, 5-year survival was better for children and adolescents than adults group (Crocetti et al., 2012). Survival decrease with increasing age was a common pattern for glial tumors.

Otherwise, Tumor location seems to have also a prognostic value: the infratentorial tumors showed a longer survival rate. This could be explained by the common location of malignant glioma is supratentorial.

High grade tumors predicted poorer survival when compared with low grade tumors (Arshad et al., 2010). In this study, the median survival among patients with high grade glioma was 6 months, with 1-, 2-, and 5-year survival rates of 19%, 12%, and 10%, respectively. Whereas, Survival was significantly better in low grade glioma with 1, 2, and 5 year survival respective rate of 22%, 20% and 17%.

Furthermore, according to therapeutic strategy, surgical resection followed by palliative treatment was significantly associated with prolonged survival then merely surgical resection.

Conclusion, glioma tumors represent a heterogeneous group with great differences in terms of frequencies and prognosis. From our data, the factors independently associated with prolonged survival are younger age at presentation, lower grade, infratentorial tumor location and palliative treatment. Moreover, statistic correlation



confirms that patients with low grade lesions have younger age. Meanwhile, high grade glioma commonly occurs during adulthood. These findings could help to guide treatment and prognosticate survival for Tunisian glioma patients.

More importantly, by focusing on the incidence estimations, our population showed an increase of high grade gliomas specifically glioblastoma rate among adult in the last period. According to their malignancy and high frequency, glioblastoma subtype should take a part of a better diagnosis investigations and healthcare management in Tunisia.

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