

RESEARCH COMMUNICATION

Trends and Morphology of Central Nervous System Malignancies in Karachi

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Abstract

Introduction: This study was conducted to assess the patterns of primary central nervous system (CNS) malignancies in Karachi South (KS), a moderate risk population in Asia. **Materials and Methods:** Data for 321 registered cases were reviewed and analyzed in two periods 1995-1997 (111 cases, 75 (67.6%) male (M); 36 (32.4%) female (F)) and 1998-2002 (210 cases, 124 (59.1%) M; 86 (40.9%) F). **Results:** Age standardized incidence rate per 100,000, crude incidence rate and relative frequency in 1995-1997 were 3.5, 2.8 and 3.5% (M) and 1.8, 1.6 and 1.7% (F). Corresponding figures for 1998-2002 were 3.3, 2.7 and 2.7% (M) and 3.3, 2.7 and 2.1% (F). Mean age of male and female patients during 1995-1997 was 33.3 years (SD± 20.4) and 30.7 years (SD±19.6). Mean ages for 1998-2002 were 33.2 years (SD±19.5) and 28.7 years (SD±18.5) for males and females respectively. In males, 199 malignancies were reported, 106 (86.9%) cases in the brain, 10 (5.5%) in meninges and 12 (6.0%) in the spinal cord; 122 cases were observed in females, 177 (89%) cases in the brain, 8 (6.6%) each in the meninges and spinal cord. The most common morphology was astrocytoma (72 (36.2%) (M); 40 (32.7%) (F)). Mean age of low grade astrocytoma was 27.8 years (M) and 27.0 years (F); anaplastic astrocytomas, 40.5 years (M), 34.1 years (F) and glioblastoma, 45.7 years (M) and 38.3 years (F). Youngest cases were registered for cerebellum and brain stem. **Conclusion:** The incidence of CNS malignancies is stable in males and gradually increasing in females. Astrocytoma is the commonest morphology; they affect a younger age group and show an age gradient in proportion to tumor grade. The mean age varied by sub-site and histology. Focus should be directed towards the understanding the biological nature and risk factors prevalent in this population.

Keywords: Brain and spinal cord cancers - Karachi, Pakistan - trends - morphology

Asian Pacific J Cancer Prev, 12, 2013-2017

Introduction

Central nervous system (CNS) tumors refer to neoplasms that originate in the brain and spinal cord of which over 90% are located in the brain. CNS malignancies account for approximately 1.7% of new cancers annually (Parkin et al., 2005). The traditional source of global descriptive data on all malignancies including CNS tumors has been the International Agency for Research on Cancer (IARC) through its series 'Cancer Incidence in the Five Continents (CIV) and the GLOBOCAN estimates for all regions of the world (Parkin et al., 2002; Curado et al, 2007; Ferlay et al., 2010). The IARC includes only population-based data of malignant tumors, from well established cancer registries all over the world. Data comparison will be based on this source.

The data represents the population of a single district of Pakistan, a low resource country in south central Asia. Pakistan shares international geographical boundaries

and cultural similarities with India, Iran, Afghanistan, China and Soviet Central Asian Republics. This cross-cultural heritage is reflected in the country's emerging cancer patterns. Karachi, the largest, southern city of Pakistan, (latitude: 24°-56'-00" and longitude: 67°-01'-00") is divided into 5 districts, South, Central, West, East and Malir. Karachi South (KS) our catchment area is the southern-most district of the city and has a fair representation of all ethnicities and socio-economic categories of Pakistan. The district has a fairly good accessibility and availability of diagnostic services within and in adjacent districts of the city. In the absence of a national cancer registration system it qualifies as a sample population of the country.

The current study was conducted to assess the incidence and trends in incidence of primary CNS malignancies in Karachi with reference to age, gender, topography and tumor morphology at diagnosis for the period 1995-2002 and compare with contemporary data.

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Materials and Methods

Epidemiological data of primary malignant tumors of the Central Nervous System (CNS) [ICD-10 (International Classification of Diseases 10th Revision) categories C71-C72], registered at Karachi Cancer Registry (KCR) for Karachi South (KS), during 1st January 1995 to 31st December 2002 were reviewed and analyzed as two time periods 1995-1997 and 1998-2002, coinciding with CIV volumes 8 and 9 (Bhurgri et al., 2000; Parkin et al, 2002; Curado et al, 2007). Pilocytic astrocytoma, benign CNS tumors, tumors of the pituitary gland and tumor-like conditions (cysts) were excluded from the analyses.

The study included clinically diagnosed and microscopically verified cases. Histologically verified cases were evaluated on hematoxylin and eosin (H&E) stained sections. Special stains (PAS, reticulin) and immunohistochemistry [ASMA, B and T cell markers, chromogranin, cytokeratin (AE1/AE3, CAM 5.2, and MNF), desmin, EMA, GFAP, MIC-2, MNF, neurofilament, NSE, S-100, synaptophysin and vimentin] were selectively used.

Manual and computerized validity checks for the cancer data were performed as per recommendations of the International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR) (Parkin, 1994). These included checks for multiple primaries and duplication. Cases were categorized by tumor site, age and sex of the patients. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grade, stage and date of death/last follow-up. Data were classified using ICD-O3 (International Classification of Diseases-Oncology, 3rd edition), WHO classification of CNS malignancies and computerized using a customized version of CANREG-4 software. Astrocytomas were categorized as low grade (grade 1 and 2) and high grade (anaplastic astrocytoma, grade 3 and glioblastoma, grade 4).

Crude, age standardized incidence rate (ASR) and age specific incidence rates were calculated using the person years of population at risk by sex and 5-year age-groups, based on the 1998 census; population of 893,684 males and 794,920 females, assuming an annual growth rate of 1.94%, as calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population, the 'world' population with a given 'standard' age distribution (Segi, 1960). The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population averaged over the number of years for which data are presented'. Incidence tables were based on ICD-10 (WHO, 1992). Data were analyzed using SPSS 19.0.

Results

Three hundred and twenty one primary CNS malignancies were registered at the Karachi Cancer Registry (KCR) for Karachi South in the eight year period from 1st January 1995 to 31st December 2002. A hundred

Table 1. Distribution of Primary Central Nervous System Malignancies (1995-2002)

Characteristic	Males	Females
Sub site (ICD-O3)		
Meninges (C700-9)	10 (5.0)	8 (6.6)
Cerebrum (C710)	34 (17.1)	9 (7.4)
Frontal lobe (C711)	22 (11.1)	13 (10.7)
Temporal lobe (C712)	16 (8.0)	11 (9.0)
Parietal lobe (C713)	15 (7.5)	9 (7.4)
Occipital lobe (C714)	-	1 (0.8)
Ventricles (C715)	2 (1.0)	2 (1.6)
Cerebellum (C716)	36 (18.1)	27 (22.1)
Brain stem (C717)	13 (6.5)	6 (4.9)
Brain, overlapping (C718)	25 (12.6)	17 (13.9)
Brain, NOS (C719)	14 (7.0)	12 (9.8)
Spinal cord (C720-9)	12 (6.0)	8 (6.6)
Morphology (ICD-O3)		
Glioma (M9380-2)	23 (11.6)	10 (8.2)
Ependymoma (M9391-3)	14 (7.0)	9 (7.4)
Astrocytoma (M9400-20)	72 (36.2)	40 (32.7)
Glioblastoma (M9440-2)	35 (17.6)	25 (20.4)
Oligodendroglioma (M9450-1)	16 (8.0)	9 (7.4)
Medulloblastoma (M9470-3)	18 (9.0)	11 (9.0)
Meningioma (M9530)	11 (5.5)	8 (6.6)
Neuroblastoma (M9500)	-	2 (1.6)
Hemangiosarcoma (M9120)	1 (0.5)	1 (0.8)
Malignant neoplasm, not otherwise specified	9 (4.5)	7 (5.7)
Total	199 (100)	122 (100)

and eleven [75 (67.6%) male; 36 (32.4%) female] cases were registered in 1995-1997; 210 [124 (59.1%) male; 86 (40.9%) female] cases were registered in 1998-2002. The overall male to female ratio was approximately 2:1. The age standardized rate (ASR) world per 100,000, crude incidence rate (CIR) and relative frequency in 1995-1997 were 3.5, 2.8 and 3.5% in males and 1.8, 1.6 and 1.7% in females respectively. The corresponding figures for 1998-2002 were 3.3, 2.7 and 2.7% for males and 3.3, 2.7 and 2.1% in females (Bhurgri et al., 2002; 2007).

The mean age of male and female patients diagnosed during 1995-1997 was 33.3 years [95%CI 28.6, 38.0; SD± 20.4; range 78 (4-82) years] and 30.7 years [95%CI 24.1; 37.3, SD±19.6, range 81 years (4-85)] respectively. Corresponding mean ages for the period 1998-2002 were 33.2 years [95%CI 29.7, 36.6; SD±19.5; range 72 (1-73)] and 28.7 years [95%CI 24.7, 32.7; SD±18.5; range 67 (3-70)] for males and females respectively. The topography and morphology of the CNS tumors was analyzed with gender stratification. A hundred and ninety nine primary CNS malignancies were reported in males during the entire eight year period (1995-2002), 106 (86.9%) cases were observed in the brain, 10 (5.5%) cases in the meninges and 12 (6.0%) cases in the spinal cord. A hundred and twenty two cases were observed in the females in that period, 177 (89%) cases in the brain, 8 (6.6%) cases each in the meninges and spinal cord. The topographical distribution of the malignancies is given in Table 1. The most common morphology was astrocytoma [72 (36.2%) cases in males; 40 (32.7%) cases in females], followed by glioblastoma [35 (17.6%) males; 25 (20.4%) females]. The morphological distribution is given in Table 1.

Discussion

Karachi South (KS) is a moderate risk population for CNS malignancies graded by the GLOBOCAN scale of I-V (Ferlay J et al, 2010). The incidence (ASR world per 100,000) of CNS tumors in KS for the period 1995-1997 was 3.5 (males) and 1.8 (females) and in 1998-2002 it was 3.3 (males) and 2.7 (females) (Bhurgri et al., 2002; 2007). Estimates of incidence for CNS malignancies differ depending upon the inclusion or exclusion of benign tumors, the quality of pathological reporting and quality of data registration. The current data includes only malignant CNS tumors.

Worldwide, the highest incidence of CNS malignancies is observed in developed areas (Australia/New Zealand, Europe, and North America) and the lowest in Africa and the Pacific islands (Parkin et al., 2005). The highest incidence (ASR world per 100,000) in 1995-1997 was reported for Croatia (9.3), Australia and Spain (8.5) in males and for Italy (7.1), China and Uruguay (6.8) in females. The lowest incidence was reported for Gambia (0.1), Viet Nam (0.7) and Uganda (0.8) in males and Uganda (0.4), Gambia (0.2) and Mali (0.1) in females (Parkin et al., 2002). The highest incidence in 1998-2002 was reported for Croatia (10.2), Poland (9.7) and Italy (9.4) in males and Poland (8.3), Croatia (7.9) and Serbia (7.5) in females. The lowest incidence (ASR world per 100,000) was reported for Uganda (0.6), Algeria (0.7) Thailand (1.1) in males and Uganda (0.7) and Bahrain (0.9) in females (Curado et al., 2007). The availability of diagnostic facilities is of immense importance in determining the incidence of CNS malignancies. The low incidence in developing countries maybe an artifact atleast partly reflecting lack of diagnostic facilities (Parkin et al., 2005).

Time trends in KS show that between 1995-1997 and 1998-2002 the incidence of CNS tumors in males remained stable and nearly doubled in females, indicating probably better accessibility to diagnostic centers for females in the latter period. Yet, there are concerns that the increase in the incidence may be genuine. This concern was also raised by Yeole from India in 2008 and Moore et al in 2010. Table 2 shows a similar trend for CNS malignancies in the Indian cancer registries as observed in KS (Parkin et al, 2002; Curado et al, 2007). Despite a rising incidence in females, CNS malignancies were twice as common in males. It is generally observed that men experience higher rates of primary brain tumors than women, with the exceptions of meningiomas, which affect 80% more females than males, and tumors of cranial and spinal nerves, and the sellar region, which affect males and females almost equally (Surawicz et al., 1999).

Gliomas in KS affected about 20% more males than females as compared to an approximately 40% preponderance reported by Kleihues and Ohgaki, showing a relatively higher component of gliomas in females in this population. Gender differences have been reported for astrocytomas especially glioblastoma which appear around the age of menarche, peak near the age of menopause, and decrease thereafter, suggesting a protective effect of female hormones (McKinley et al., 2000). In KS this

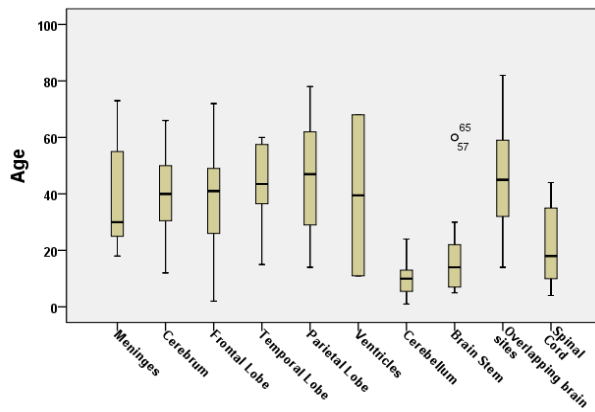


Figure 1. Mean age at Presentation of Central Nervous System Malignancies by Topography

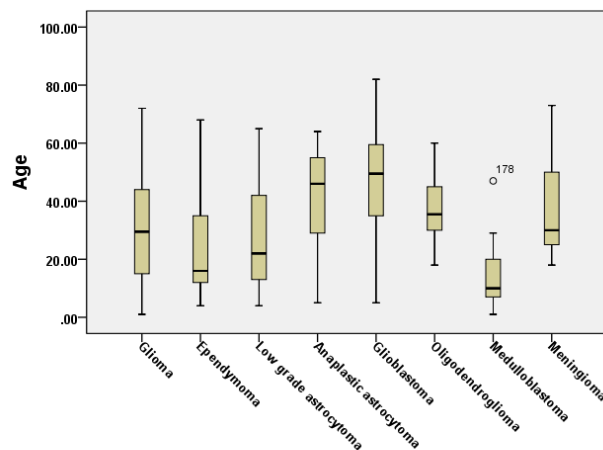


Figure 2. Mean age at Presentation of Central Nervous System Malignancies by Morphological Sub-type

The mean age varied by sub-site of tumor origin (Figure 1) and morphology (Figure 2). The youngest cases were registered for cerebellum and brain stem. The oldest patients were observed with temporal lobe lesions and those with advanced lesions involving more than one lobe. Overall, the first cases were observed in infants (0-4 year age group) and continued throughout life (table 5). The peak incidence of CNS malignancies was observed between 50-65 years [1995-1997 males (ASR 11.6; 60 years), females (ASR 9.3, 55 years)] [1998-2002 males (ASR 11.6; 65 years) females (ASR 11.0; 50 years)].

Table 2. Age Standardized Incidence Rates (ASR) per 100,000 in Karachi South - Comparison to Indian Registries 1995-1997 and 1998-2002

Registry	1995-1997 ¹		1998-2002 ²	
	Male	Female	Male	Female
Karachi South	3.5	1.8	3.3	2.7
Ahmedabad	2.5	1.5	-	-
Bangalore	2.6	1.6	-	-
Chennai (Madras)	3.0	1.7	3.0	2.1
Delhi	4.6	3.1	4.1	2.3
Karunagappally	1.9	1.5	3.7	1.9
Mumbai	3.5	2.3	3.7	2.8
Nagpur	3.9	2.3	3.0	2.6
Poona	3.5	2.5	3.6	1.9
Trivandrum	2.4	1.8	2.9	2.2

¹Parkin et al., 2002; ²Curado et al, 2007

protective effect was not clearly apparent. The overall component of glioblastoma remained higher for females than the males. A greater focus should be directed towards the understanding of the biological nature and risk factors of gliomas. Hormone studies, inherited polymorphisms in genes related to carcinogen metabolism, and DNA repair, as well as, gene environment interactions in this population need attention as the biological behavior of the malignancies differs from the reported literature for developed countries.

CNS tumors are currently classified by histology and location. Gliomas further categorized as astrocytomas, oligodendrogliomas, and ependymomas from the cell of origin (Kleihues et al., 1995) are the commonest CNS malignancies globally accounting for approximately 70% of the cases, with glioblastomas being the most common sub-type (Ohgaki, 2009). In Karachi the component of gliomas is high, accounting for 70% overall (80% cases in men; 61% in women) cases. This pattern is similar to the pattern observed in industrialized countries and also reported by other authors from Karachi (Ahmed et al., 2004). There is a reported tendency toward a higher incidence of gliomas in highly developed, industrialized countries and some reports indicate that Caucasians have a higher incidence than African or Asian populations (Ohgaki, 2009).

Oligodendroglioma comprised 16 (8.0%) cases in men and 9 (7.4%) cases in women. This collaborates with the statistics reported by El-Zein et al. Oligodendroglioma constitutes 5–12% of all glial tumors and 5–7% of all intracranial tumors. Ependymomas accounted for approximately 7.0% of all malignant tumors, the figure being slightly higher than the reported 4–6% by El-Zein et al. Malignant meningiomas comprised 11 (5.5%) cases in men and 8 (6.6%) in women as opposed to 10–19% reported by El-Zein et al. neither did we observe the 2:1 predominance in women over men as reported by this group. Medulloblastomas constitute 3–5% of all brain tumors, but in our series they constituted 9.0% of the cases in both genders.

A cause of concern is the younger age at diagnosis. Malignancies of the CNS were observed atleast a decade earlier in KS. The mean age of male and female patients diagnosed during 1995-1997 was 33.3 and 30.7 years respectively. Corresponding mean ages for the period 1998-2002 were 33.2 and 28.7 years. Internationally the mean age at onset is reported as 54 years (McCarthy et al., 2002). An overall peak incidence of age 60 years has been reported by Kleihues and Ohgaki in 2000. In KS, the peak incidence of CNS malignancies was observed between 50-65 years, with the females showing a peak 5 years earlier than males.

A variation in the mean age has been reported for each histological category (McCarthy et al., 2002) and for each of these categories the mean age observed in KS was a decade or so younger. This variation cannot be attributed to differing diagnostic practices or a lack of accessibility to diagnosis, as in that situation we would have experienced older age groups at diagnosis. The mean age of low grade diffuse astrocytoma was 27.8 years in males (M) and 27.0 years in females (F), for anaplastic astrocytomas it was

40.5 years M, 34.1 years F and for glioblastomas it was 45.7 years (M) and 38.3 years (F). The reported mean age is 34 years for low grade diffuse astrocytoma (Kleihues et al., 1997); 41 years for anaplastic astrocytoma (Davis et al., 1997) and 53 years for glioblastoma (Kleihues et al., 1997b). The mean age at onset for meningiomas is reported as 62 years (McCarthy et al., 2002) whereas in Karachi it was 38.6 in men and 43 years in women.

In conclusion, tumors of the brain are not uncommon malignancies. They are aggressive and even the better differentiated tumors have a high morbidity and mortality. Karachi South (KS) is a moderate risk population for CNS malignancies. The morphological distribution is similar to the pattern observed in industrialized countries. The overall component of glioblastoma remained higher for females than the males. Time trends in KS show a stable incidence in males and an increase in females. A cause of concern is the younger age at diagnosis. A greater focus should be directed towards the understanding of the biological nature and risk factors of gliomas.

Acknowledgements

The authors declare that there is no conflict of interest with this work.

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