

Original Article

The Evangelismos hospital central nervous system tumor registry: Analysis of 1414 cases (1998-2009)

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Abstract

Background: The Evangelismos Hospital central nervous system (CNS) Tumor Registry represents the current effort of the Departments of Neurosurgery and Pathology to collect data for primary and metastatic CNS tumor patients. In the present study, 12-year hospital data (1998-2009) were reviewed and analyzed.

Methods: Patients that underwent surgery for CNS tumors for the first time were identified. Histologically confirmed tumor rates by age and gender were compared. Time trends in annual rates for specific tumor types were investigated. In-hospital mortality rates and length of hospital stay were analyzed by age and gender and their putative variations across the study period investigated.

Results: A total of 1414 patients (age 15-89 years) were identified. The most frequently encountered histologies were gliomas and meningiomas, accounting for, respectively, 32.8% and 29.1% of the total sample. A greater proportion of meningiomas was found in women; the proportion of glioblastomas and metastatic tumors, as well as of mixed gliomas, were greater in men. Increased rates of glioblastoma and meningioma with advancing age at diagnosis were also apparent. There were no significant variations in time trends for specific tumor types. In-hospital mortality was significantly higher for older patients (≥ 70 years). An increase in the length of hospital stay was apparent between the first and middle third of the study period.

Conclusions: Analysis of tumor rates in relation to age at diagnosis and gender showed significant bias in accordance with salient literature. Available data indicated no significant variations in time trends for specific tumor types across the study period, while an adverse effect of advanced age on in-hospital mortality was shown. The present findings can guide the formulation of future treatment programs and preventive strategies and provide the basis for further intra- and/or interdepartmental research.

Key Words: Central nervous system tumors, hospital-based tumor registry, length of hospital stay, mortality, surgical mortality

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INTRODUCTION

Central nervous system (CNS) tumors comprise a highly complex, heterogeneous group of neoplasms exhibiting great diversity in histological traits, patterns of growth, recurrence, and treatment response.^[1,5,7,33,43] While their overall incidence compared with tumors on other sites of the human body is relatively low, CNS tumors represent a significant public health issue in both Europe and the United States.^[18,19,21,31] In this context, time trends in the incidence of CNS tumors remains a topic of considerable interest and debate. The results of several European and North American studies on temporal trends in the incidence of CNS tumors suggest that the apparent trend toward increased incidence observed in the late 1980s and early 1990s, a period characterized by the use of improved diagnostic means, is reaching a plateau and may even be declining.^[11-14,22,24,28,30,32]

Given that a national registry on CNS tumors in Greece has not yet been established, epidemiological analysis on this clinical entity remains a significant challenge. Toward this direction, the Departments of Neurosurgery and Pathology at Evangelismos Hospital, the largest general hospital in Greece,^[41] are committed to the generation and maintenance of an electronic tumor registry for the evaluation of health care provision, the analysis of health trends and formulation of future treatment programs and preventive strategies. In the present study, our 12-year hospital data (1998-2009) were reviewed and a total of 1414 patients that were treated for CNS tumors for the first time, identified. To our knowledge this is the first report on data incorporating all major tumor types from a large series of patients (age 15-83 years), in Greece. We specifically aimed in establishing: (i) Rates of histologically confirmed tumors by age and gender, (ii) time trends of annual rates for specific tumor types, and (iii) in-hospital mortality rates and hospitalization times in relation to patient's age and gender and their putative variations across the study period.

MATERIALS AND METHODS

This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Data collection and tumor classification/staging

The Evangelismos Hospital CNS Tumor Registry (ECTR) represents the current effort of the Departments of Neurosurgery and Pathology to collect data in an electronic format for all primary and metastatic CNS tumor patients from 1998 onwards. Data drawn from the respective departmental databases incorporating patient demographic characteristics, tumor histological types, and surgical outcome are combined within a single database. Tumor classification data are based on International Classification of Diseases for Oncology (ICD-O) histology,

as described previously.^[25] Meningioma and glioma staging are based on World Health Organization (WHO) 1993.^[27] Tumors of the scalp and skull as well as all infectious, inflammatory, vascular, and peripheral nerve lesions were excluded from the present analysis.

Statistical analysis

Continuous variables are presented with mean and standard deviation (SD) and/or median (interquartile range = IQR). Qualitative variables are presented with absolute and relative frequencies. Chi-square tests for homogeneity were used to evaluate differences in tumors rates over the years. *P* values for trends in tumors rates over the ordered categories of age groups were also computed. For in-hospital mortality, Pearson's Chi-square tests were also used to evaluate differences in proportions between men and women, age groups and time periods. Mann-Whitney tests were used for the comparison of hospital stay between two groups. For the comparison of in-hospital mortality rates between all different tumors categories, Bonferroni correction for the control of type I error was implied and only differences with *P* values less than 0.001 are presented. All *P* values reported are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 17.0).

RESULTS

Patient demographic characteristics

A total of 1414 patients (49.7% men and 50.3% women) with a mean age of 55.4 years (SD = 14.4 years) were identified over the 12-year study period (1998-2009). Thirteen patients between the age of 15 and 18 years (13/1414, 0.9%), treated in our department were incorporated in the present analysis. The majority of patients (51.3%) aged between 52 and 70 years; 26.9% of patients aged between 33 and 51 years while 7.6% of patients aged less than 33 years. Among those, 1351 patients (95.5%) had newly diagnosed, histologically confirmed tumors while 63 patients (4.5%) remained undiagnosed due to failure of biopsy procedures. Intracranial localization of tumors was evident in the vast majority of cases (93%, *n* = 1315); a small proportion (7%, *n* = 99) showing spinal origin. All patients underwent either a craniotomy or laminectomy for total or partial tumor excision or diagnostic biopsy.

Histological findings and annual incidence rates

The relative frequencies of the major histological categories in the ECTR are shown in Figure 1. All histological types according to age groups and gender are presented in Table 1. Meningiomas and glioblastomas were the most frequently encountered types, each accounting for, respectively, 29.1% (412/1414) and 16.3% (231/1414) of all cases. A highly significant trend for increased glioblastoma and meningioma tumors

rates with advancing age at diagnosis was apparent ($P < 0.001$). A greater proportion of meningiomas was found in women (290/711; 40.8%) compared with men (122/703; 17.4%) $P < 0.001$. The proportion of glioblastomas and metastatic tumors ($P < 0.001$) as well as of mixed gliomas ($P < 0.05$), were greater in men [Table 1]. The most common primary cause of metastases was lung cancer (51%).

Table 2 shows patient characteristics by WHO grade classification (gliomas and meningiomas). WHO IV was the most frequent histological type among gliomas (62.9%). Considering tumor frequency among different age groups [Table 2], WHO I, II, not otherwise specified (NOS) gliomas and WHO I meningiomas appear more frequently in the youngest age groups, whereas WHO IV gliomas were more frequent in older ages ($P < 0.001$). Additionally, WHO I meningiomas were

more frequent in women than men. Figure 2 shows the annual percentage of gliomas (glioblastomas and nonglioblastomas), meningiomas, and metastases across the study period (1998-2009). No significant differences were found in the rates of any histologically diagnosed tumor types during the 12 years.

In-hospital mortality rates and hospitalization time

Table 3 shows in-hospital mortality rates for patients in different tumor subcategories. The mortality rate for the total sample was 5.4% (76/1414), ranging from 1.1% (1/92) for nerve sheath tumors to 8.7% (2/23) for lymphomas; rates were not significantly different between the 7 tumor categories. In-hospital mortality for intracranial tumors was 5.8% (76/1315). In-hospital mortality was significantly higher for older patients (age ≥ 70 years; 21/242 (8.7%) vs. age <70 years; 55/1172 (4.7%) $P = 0.012$). There were no

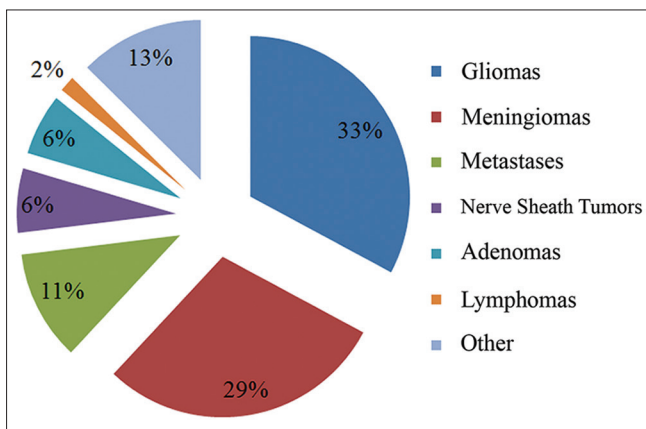


Figure 1: The pie diagram represents the relative frequencies according to histopathological tumor types (Evangelismos Hospital CNS Tumor Registry: 1998–2009)

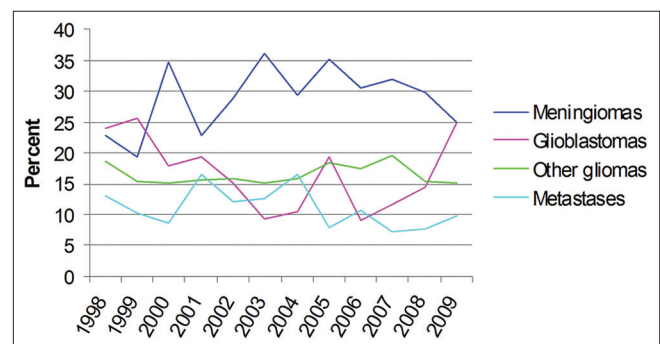


Figure 2: Linear histogram depicting the annual percentage of patients diagnosed with four of the common tumor types identified in our registry namely glioblastomas, other gliomas (including oligoastrocytomas and other non WHO grade IV astrocytic tumors), meningiomas and metastases that were hospitalized in the neurosurgery clinic of Evangelismos hospital between 1998 and 2009

Table 1: Age and gender distribution of brain tumor patients in the Evangelismos hospital according to histopathology

Tumor type	Age (years)				P*	Sex		P**	Total
	15-32	33-51	52-70	71-89		Women	Men		
	N (%)	N (%)	N (%)	N (%)		N (%)	N (%)		
Glioblastomas	3 (2.8)	53 (13.9)	130 (17.9)	45 (22.5)	<0.001	87 (12.2)	144 (20.5)	<0.001	231 (16.3)
Astrocytic	16 (14.8)	13 (3.4)	26 (3.6)	7 (3.5)	0.001	26 (3.7)	36 (5.1)	0.179	62 (4.4)
Oligodendroglial	2 (1.9)	18 (4.7)	19 (2.6)	3 (1.5)	0.157	18 (2.5)	24 (3.4)	0.329	42 (3.0)
Mixed gliomas	4 (3.7)	12 (3.1)	37 (5.1)	8 (4.0)	0.401	23 (3.2)	38 (5.4)	0.045	61 (4.3)
Ependymomas	6 (5.6)	5 (1.3)	2 (0.3)	2 (1.0)	<0.001	7 (1.0)	8 (1.1)	0.778	15 (1.1)
Gliomas-NOS	13 (12.0)	12 (3.1)	24 (3.3)	4 (2.0)	0.001	26 (3.7)	27 (3.8)	0.856	53 (3.7)
Meningiomas	10 (9.3)	114 (29.9)	211 (29.1)	77 (38.5)	<0.001	290 (40.8)	122 (17.4)	<0.001	412 (29.1)
Metastases	2 (1.9)	31 (8.1)	102 (14.1)	22 (11.0)	0.001	48 (6.8)	109 (15.5)	<0.001	157 (11.1)
Nerve sheath tumors	13 (12.0)	25 (6.6)	48 (6.6)	6 (3.0)	0.010	50 (7.0)	42 (6.0)	0.420	92 (6.5)
Adenomas	2 (1.9)	36 (9.4)	46 (6.3)	4 (2.0)	0.120	40 (5.6)	48 (6.8)	0.350	88 (6.2)
Lymphomas	1 (0.9)	3 (0.8)	14 (1.9)	5 (2.5)	0.089	14 (2.0)	9 (1.3)	0.306	23 (1.6)
Other ^a	36 (33.3)	59 (15.5)	66 (9.1)	17 (8.5)	<0.001	82 (11.5)	96 (13.7)	0.229	178 (12.6)
Total	108 (100.0)	381 (100.0)	725 (100.0)	200 (100.0)		711 (100.0)	703 (100.0)		1414 (100.0)

*P values for trend, **Chi-square test, ^aCategory incorporating rare tumors (epidermoid cysts, choroid plexus papillomas, craniopharyngiomas, hemangioblastomas, medulloblastomas/PNET, paragangliomas, pineal tumors)

Table 2: Number of cases according to the age-distribution and world health organization grading for gliomas and meningiomas

Tumor type	Age (years)				P	Sex		P	N (%)
	15-32	33-51	52-70	71-89		Women	Men		
	N (%)	N (%)	N (%)	N (%)		N (%)	N (%)		
Gliomas									
WHO I	8 (20.0)	2 (1.9)	1 (0.4)	2 (2.9)	<0.001	8 (4.4)	5 (1.9)	0.113	13 (2.9)
WHO II	13 (32.5)	17 (16.0)	12 (5.2)	5 (7.2)	<0.001	13 (7.2)	34 (12.7)	0.062	47 (10.5)
WHO III	3 (7.5)	13 (12.3)	33 (14.2)	4 (5.8)	0.842	25 (13.9)	28 (10.5)	0.275	53 (11.9)
WHO IV	3 (7.5)	62 (58.5)	162 (69.8)	54 (78.3)	<0.001	108 (60.0)	173 (64.8)	0.304	281 (62.9)
NOS ^a	13 (32.5)	12 (11.3)	24 (10.3)	4 (5.8)	<0.001	26 (14.4)	27 (10.1)	0.165	53 (11.9)
N/A*	4	7	6	0		7	10		17
Meningiomas									
WHO I	9 (90.0)	69 (60.5)	120 (56.9)	39 (50.6)	0.040	177 (61)	60 (49.2)	0.026	237 (57.5)
WHO II	1 (10.0)	37 (32.5)	77 (36.5)	32 (41.6)	0.063	96 (33.1)	51 (41.8)	0.092	147 (35.7)
WHO III	0 (0.0)	2 (1.8)	2 (0.9)	0 (0.0)	0.324	0 (0.0)	4 (3.3)	0.107	4 (1.0)
NOS ^a	0 (0.0)	6 (5.3)	12 (5.7)	6 (7.8)	0.343	17 (5.9)	7 (5.7)	0.961	24 (5.8)

*N/A: No available grading data, ^aNOS: Not otherwise specified, WHO: World health organization

Table 3: In-hospital mortality rates in major tumor categories

Tumor type	Mortality N/Total N (%)
Gliomas	22/464 (4.7)
Meningiomas	31/412 (7.5)
Metastases	8/157 (5.1)
Nerve sheath tumors	1/92 (1.1)
Adenomas	2/88 (2.3)
Lymphomas	2/23 (8.7)
Other	9/178 (5.1)
Total	76/1414 (5.4)

gender-related differences in in-hospital mortality rates.

The median number of hospital days for total sample was 16 (IQR: 11-25). There was a significant increase ($P < 0.001$) of hospital stay from 1998-2001 (median = 15 days, IQR 11-23) to 2002-2005 (median = 18 days, IQR 12-27). Hospitalization time did not vary significantly from 2002-2005 to 2006-2009 (median = 17 days, IQR 11-26). There was no age (70 years cut-off) or gender-related differences in hospitalization time. In-hospital mortality rates did not vary significantly between the three consecutive 4-year periods.

DISCUSSION

The Departments of Neurosurgery and Pathology at Evangelismos Hospital are committed to the generation and maintenance of an electronic CNS tumor registry (ECTR that allows for the evaluation of health-care provision, the analysis of health trends,

and formulation of future treatment programs and preventive strategies). In the present study, we analyzed our 12-year data, incorporating a total of 1414 patients (age 15-83 years) that were treated for CNS tumors for the first time. To our knowledge this is the first report on data incorporating all major tumor types from a large series of patients in Greece. A previous study has provided population-based data on cerebral gliomas in a defined Northwest area of Greece,^[20] while another study has recently provided hospital-based data on the frequency of pediatric brain tumors (<15 years old).^[2]

The present findings indicated that meningiomas and glioblastomas were the most frequently encountered primary CNS tumors, accounting for, respectively, 29.1% ($n = 412$) and 16.3% ($n = 231$), followed by nerve sheath tumors ($n = 92$, 6.5%) and adenomas ($n = 88$, 6.2%). The relatively low percentage of metastases ($n = 157$, 11%) and lymphomas ($n = 23$, 1.6%) in our series may be due to the exclusion of cases that are considered inoperable and thus treated solely with chemotherapy or radiation. As a corollary, higher rates for metastases and lymphomas are typically reported in neurooncology series.^[17] Of note is that the relative frequency of the major histopathologies in ECTR is similar to that of population-based registries, such as the Central Brain Tumor Registry of the United States (CBTRUS)^[8,9] and the Austrian National Cancer Registry (ABTR).^[42]

Our analysis of tumor rates by age and gender indicated significant bias. The present findings of significantly higher rates for meningiomas in women, a male predominance for glioblastomas, and increases in the incidence rates for glioblastoma and meningioma with advancing age at diagnosis, are consistent with the preponderance of

evidence provided by salient epidemiological studies and reports.^[3,6,8-11,13-15,22-24,26,28,30,32,35,42]

Given changing trends in diagnostic technique and tumor classification, analyses of time trends in the incidence of histologically defined tumors remains a significant challenge.^[16,22,28,34] Time trend analysis of annual rates for specific tumor types indicated no significant variation across the study period. A rather steady incidence rate for meningiomas appears consistent with previous findings on Northern European and Balkan populations during overlapping time periods.^[13,15] Moreover, a flat trend in the incidence of glioma for the whole of Europe, during the period 1995-2002, was recently shown.^[11]

In-hospital mortality was another parameter analyzed in the present study. Our results indicated an overall in-hospital mortality rate of 5.4% (ranging between 1.1% for nerve sheath tumors and 8.7% for lymphomas). The in-hospital mortality for brain tumor patients was 5.8%. The Department of Neurosurgery^[41] at Evangelismos Hospital represents a high volume unit (over 150 craniotomies/year). Nevertheless, it is noteworthy that the rate of in-hospital mortality in the present series is only comparable to that of low volume US hospitals (<50 craniotomies/year) and considerably higher than that of high-volume specialized US units.^[4,10,31,38] Moreover, the length of hospital stay in the present series (median: 16 days) is relatively high compared with previous estimates on US units.^[4,10,31,38]

Examining the impact of age on in-hospital mortality rates, the present findings indicated significantly higher mortality rates for older patients (70 years cut-off point). This finding appears consistent with previous evidence indicating that advanced age has an adverse effects on neurosurgical mortality rates in tumor patients.^[4,10,29,33,40] Nevertheless, it should be noted that age alone cannot be safely used as a selection criterion for surgery.^[37,39] While beyond the scope of the present analysis, future studies incorporating adjustments for factors such as tumor size/location and histological characteristics, preoperative neurological, and physical status, co-morbidities^[6,36,38,40] are warranted.

CONCLUSIONS

This is the first report on data incorporating all major CNS tumor types from a large cohort of patients (N = 1414, age 15-83 years), in Greece. Analysis of histologically characterized tumors in relation to age at diagnosis and gender showed significant bias in accordance with salient literature. Available data indicated no significant variations in time trends for specific tumor types across the 12-year study period, while an adverse effect of advanced age (≥ 70 years) on in-hospital mortality was shown. Data on hospital stay indicated relatively long hospitalization times and an

increase in the length of hospital stay between the first and middle third of the study period. The present finding can guide the formulation of future treatment programs and preventive strategies and provide the basis for intra- and/or interdepartmental research.

We would strongly encourage other neurosurgical centers to foster interdepartmental collaborations in order to collect, analyze, and publish equivalent data that could form the basis for a future national population-based registry. In this regard, it is noteworthy that CNS tumor population incidence rates for Greece are currently estimated on the basis of the national mortality for 2008 by means of modeling, using a set of age, sex, and site-specific incidence mortality ratios obtained by the aggregation of recorded cancer registry data from the cancer registries of neighboring countries.^[18] Future studies aimed in determining population-based incidence rates within well-defined cohorts as well as patient follow-up in order to determine factors influencing outcome, functionality, recurrences, and survivorship are also clearly warranted.

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