Epidemiology of Central Nervous System Tumors in Labin Area, Croatia, 1974-2001

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Aim. To establish the incidence of tumors of the central nervous system (CNS) in the population of Labin area in Istria, Croatia, characterized by very little population migration.

Method. We retrospectively analyzed data on 175 patients (102 men and 73 women) diagnosed with CNS tumor according to the World Health Organization’s diagnostic criteria in the period 1974-2001. Patient data were retrieved from multiple sources: files of general practitioners in Labin area; registers of admissions and discharges of the Pula General Hospital and Rijeka University Hospital Center; and medical records of the Hospital Departments of Neurology, Surgery, Neurosurgery, Oncology and Radiotherapy, and Pathology. Annual incidence, anatomic location, and pathohistological classification of CNS tumors were determined, as well as age at disease onset.

Results. Out of 175 subjects, 95 had primary CNS tumors and 80 had metastases. Intracranial tumors were found in 88.4% of patients with primary CNS tumors (annual incidence, 11.8/100,000 population) and intraspinal in 11.6% of patients (annual incidence, 1.6/100,000). Similar distribution was observed for CNS metastases (70 intracranial vs 10 intraspinal), with annual incidence of 9.9 and 1.4/100,000, respectively. The most frequent intracranial tumors were those of neuroepithelial tissue, accounting for 58.3% of all CNS neoplasms (annual incidence, 6.9/100,000 population). The most frequent intraspinal tumors were tumors of the meninges (54.5%). There was no particular temporal clustering of CNS tumors. The age at disease onset corresponded with that reported in the literature: 50.5±17.0 years for primary intracranial tumors, and 59.7±12.2 years for primary intraspinal tumors.

Conclusion. Primary CNS tumors showed high, but temporally stable incidence in population of Labin area over the last 27 years, indicating that the alleged increase in CNS tumors incidence was not true.

Key words: age of onset; astrocytoma; brain neoplasms; central nervous system neoplasms; Croatia; epidemiology; incidence; spinal cord neoplasms

Tumors of the central nervous system (CNS) are a heterogeneous group of neoplasms comprised of all forms of primary or secondary neoplasms derived from the structures within the craniovertebral cavity (1). Reports on the incidence of primary CNS tumors in Croatia are inadequate, mainly based on hospital (2) and the Croatian Cancer Registry records (3). Lately, unverified sources have been talking an alleged increase in the incidence of neoplasms in Istria (4). Thus, we decided to establish the incidence of CNS tumors in the Labin area, in Istria, to support or refute these allegations.

Subjects and Methods

Subjects

The sample consisted of 175 patients, 102 men and 73 women, diagnosed with CNS tumors according to the diagnostic criteria of World Health Organization (1). Five patients were children: four girls aged 8, 9, 10, and 11 years, and a boy of 16. The age at disease onset ranged from 8 to 83 years. All patients had been residents of the Labin area for at least five years before inclusion in the study: 127 of them were born in the Labin area and the rest were from other parts of Istria and Croatia, from Bosnia and Herzegovina, and Slovenia.

Study Area

The Labin area at the eastern coast of Istria (Fig.1) includes the town of Labin itself and the adjoining municipalities of Pican, Kršan, St. Nedelja, and Raša. Despite occasional migrations (<5%), the number of inhabitants has been relatively stable in the last 50 years: 25,567 in 1971, 25,500 in 1981, and 25,983 in 1991 (5-7). In 2001, the population of the area was 24,131, with 11,775 men and 12,356 women (6,7). About half the population lives in urban, and the other half in rural parts of the area, in settlements ranging from a few to several thousand inhabitants. The economy of the Labin area was once based on the exploitation of pit coal, cement production, thermonuclear power plant, several smaller metallurgical plants, tourism, and to a lesser extent agricultu-
Health Care System

Health care in the Labin area is among the best in Croatia. The Labin Health Center, an institution of primary health care of semi-urban type, comprises 14 general (family) medicine offices, with physician-to-patient ratio ranging from 1:200 to 1:700, an office for preschool children, a gynecologic outpatient clinic, and 10 dental outpatient clinics. There are also a diagnostic radiology unit, hemato-biochemical laboratory, emergency unit with 25 beds, dialysis center, school medicine service, occupational medicine service, and epidemiological service. There are four pharmacies in the area. The Center is also an educational institution and serves as a primary health care training center for Rijeka University Medical students and interns.

The population of the Labin area mainly gravitates toward the General Hospital in Pula and Rijeka University Hospital Center in Rijeka, and only occasionally to Zagreb hospitals (up to 1990, they also went to Ljubljana hospital in neighboring Slovenia). Institutes of Public Health of the Counties of Istria and Primorje-Gorski Kotar are also located in Pula and Rijeka, respectively. Rijeka University Hospital Center has been equipped with a computedized tomography equipment (CT) since 1986, and General hospital in Pula since 1992. The nuclear magnetic resonance (NMR) examinations are carried out in Zagreb, Valdoltra (Slovenia), and Trieste (Italy).

Data Collection and Verification of Diagnosis

The list of patients with CNS tumors was compiled from the Death Register and the Cancer Incidence Register of Labin Health Center for the period 1974-2001. The data were completed through personal contact of investigators with all physicians in the area, as well as by using registers of admissions and discharges of General Hospital in Pula (Departments of Neurology and Pathology) and Rijeka University Hospital Center (Departments of Neurology, Surgery, Neurosurgery, Oncology and Radiotherapy, and Pathology).

We had free access to all health records and hospital medical histories; patient identity was strictly kept anonymous. To verify hospitalization of our study participants we also used the data from the Labin branch of Croatian Health Insurance Institute, which keeps records of all hospitalizations in the country and abroad and is responsible for approving and reimbursement of health care expenses.

Medical record card and/or clinical history of the disease were obtained for each potential patient, and pathohistological findings were obtained in cases where the remaining documentation was not assessed as reliable. All patients fulfilling the World Health Organization diagnostic criteria (1) for CNS tumors were included in the analysis. Their personal data were checked in the Labin area registry books of births and deaths, and their professions in the files of the Croatian Pension Insurance Bureau – Labin branch. The day of disease onset was the day when a patient contacted their physician for symptoms and signs characteristic of CNS tumor.

This study was approved by the Pula branch of Croatian Medical Association’s Ethics Commission.

Data Analysis

Demographic data for the Labin area were obtained from the Republic of Croatia Census for 1971, 1981, 1991, and 2001 (5-9). The average number of inhabitants per year in the 1974-2001 period was estimated by using the interpolation method (10). The same method was applied for assessing the structure of the population by age and sex for 1986, the median year of the study period. Rate standardization was performed with the direct standardization method (11) applied on the standard population of the Labin area to allow international comparison with the “new” European and world populations. Source for the “new” standard populations were the tables proposed by the World Health Statistics Annual 1992 (12). Standardization of the rates was done if the overall number of tumors was 10 or more.

Statistical Analysis

Time trends were tested with chi-square test and age at disease onset was tested with the two-sample test of means. Smith’s Statistical Package freeware (Version 2.5, August 30, 2001; http://www.economics.pomona.edu/StatSite/SSP.html) was used for all statistical analyses. Level of statistical significance was set at p<0.05.

Results

From January 1, 1974, to December 31, 2001, a total of 175 patients with CNS tumor were registered in the Labin area. In 95 cases (54.3%), the tumor was primary and in 80 (45.7%) secondary. The location of primary CNS tumors was intracranial in 84 (88.4%), and intraspinal in 11 (11.6%) cases. Metastatic tumors showed the same distribution ratio (70 intracranial vs 10 intraspinal). Apart from 13 patients with a clinical diagnosis, all other patients with primary CNS tumor underwent surgery and the diagnosis was histologically confirmed. Clinical diagnosis in 5 patients suffering from glioblastoma was supported by angiography, myelography, or a CT-scan. The diagnosis of meningiomatosis in one of the patients was established on the basis of CT-scan. Furthermore, CT-based diagnosis was combined with MRI in a female patient suffering from pineal parenchymal tumor and in 6 patients (one male and 5 female) suffering from pituitary adenoma.

The most frequent primary intracranial tumors were those of neuroepithelial origin, accounting for 58.3% of all diagnosed CNS neoplasms (Table 1). Tu-
The annual incidence or five-year incidence of primary intracranial tumors showed no particular temporal clustering either with respect to the number or histological type of tumor (Fig. 2). However, the dollars of the meninges were equally frequent among primary intracranial tumors, those of the neuroepithelial and meningeal origin were more frequent in men, whereas pituitary gland tumors were mostly diagnosed in women (Table 1).

The mean annual crude incidence for all primary intracranial tumors was 11.8/100,000 population (11.7 when standardized to Croatian population), and 1.6/100,000 population (1.5 when standardized to Croatian population) for all primary intraspinal tumors (Table 2). However, a slighty increasing trend in incidences of primary intracranial tumors (chi-square=10.6164, df=1, \( p=0.001 \)) than intraspinal (chi-square=1.7435, df=1, \( p=0.8073 \)) in women was not statistically significant. The corresponding rates for metastatic tumors were lower: 9.9/100,000 population for intracranial (9.4 when standardized to Croatian population) and 1.4/100,000 population for intraspinal metastases (1.3 when standardized to Croatian population). Metastases in men were found at higher rates in both locations, although only intracranial were significantly more frequent (chi-square=10.6164, df=1, \( p=0.001 \)) than intraspinal (chi-square=1.7435, df=1, \( p=0.8073 \)). Although the population of the Labin area is elderly, standardization with the European population showed no significant differences. However, the incidence rates among tumors with later onset in men than in women (neuroepithelial) were slightly lower in men when standardized with European population, and remained within a same range in women.

The annual incidence or five-year incidence of primary intracranial tumors showed no particular temporal clustering either with respect to the number or histological type of tumor (Fig. 2). However, the
trend for both genders, taking in account all types of tumors, increased steadily and linearly over time. The five-year incidence per 100,000 population in the periods 1974-1978, 1979-1983, 1984-1988, 1989-1993, 1994-1998, and 1999-2001 were 4.8, 17.5, 6.3, 11.0, 19.6, and 14.0 respectively for men (chi-square=9.118, df=5, p=0.104); 9.2, 6.2, 12.2, 10.7, 18.8, and 13.4 (chi-square=4.972, df=5, p=0.497) for women; and 7.0, 11.8, 9.3, 10.8, 19.6, and 13.7 for total (chi-square=9.202, df=5, p=0.101).

The mean age at disease onset (Table 3) and distribution by age (Fig. 3) were different for each particular type of intracranial tumor. However, significant differences in the age at disease onset were recorded only in male population for neuroepithelial tumors, which occurred at significantly older age than tumors of the meninges (t=3.181, df=15, p=0.003). Neuroepithelial tumors, particularly astrocytomas and glioblastomas, occurred after the third decade of life, their frequency increasing with age (Fig. 3). The astrocytomas were the most frequent in the fifth decade of life, and the glioblastomas in the sixth. Tumors of the meninges (mostly meningiomas) were present in almost all age groups, with 11 out of 17 cases occurring in 40-69 age group (chi-square=5.969, df=1, p=0.015). Furthermore, 3 out of 7 meningiomas in men and 0 out of 6 in women were diagnosed at the ages between 15 and 29, giving an incidence of 2.0/100,000 population before age 30 (1.1 when referred to total population). The incidence of pituitary gland tumors in women decreased with the decrease in their fertility. Metastatic intracranial tumors (although observed as early as the third decade of life) have almost doubled from the fifth decade of life (10.9/100,000 population) to the eight decade of life (38.6/100,000 population).

### Table 3. Mean age of the patients at the onset of the central nervous system (CNS) tumor disease in the Labin area, Croatia, 1974-2001

<table>
<thead>
<tr>
<th>CNS tumors</th>
<th>Age (years, mean ± SD) at the onset</th>
<th>Mean age difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>men</td>
<td>women</td>
</tr>
<tr>
<td>Primary intracranial:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroepithelial:</td>
<td>56.9 ± 13.7*</td>
<td>41.3 ± 17.4</td>
</tr>
<tr>
<td>astrocytic tumors</td>
<td>56.9 ± 13.8</td>
<td>48.3 ± 11.5</td>
</tr>
<tr>
<td>astrocytoma</td>
<td>53.5 ± 14.1</td>
<td>44.3 ± 13.0</td>
</tr>
<tr>
<td>glioblastoma</td>
<td>57.5 ± 14.0</td>
<td>50.4 ± 11.0</td>
</tr>
<tr>
<td>Meningeal:</td>
<td>39.6 ± 17.7*</td>
<td>54.6 ± 13.5</td>
</tr>
<tr>
<td>meningioma</td>
<td>39.4 ± 19.8</td>
<td>52.5 ± 13.5</td>
</tr>
<tr>
<td>pituitary tumors</td>
<td>35.2 ± 18.1*</td>
<td>52.5 ± 17.6</td>
</tr>
<tr>
<td>total</td>
<td>52.7 ± 16.0</td>
<td>42.6 ± 17.4</td>
</tr>
<tr>
<td>Primary intraspinal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lung tumors</td>
<td>57.8 ± 11.3</td>
<td>73.0 ± 10.9</td>
</tr>
<tr>
<td>other sites</td>
<td>63.6 ± 9.9</td>
<td>65.4 ± 15.5</td>
</tr>
<tr>
<td>total</td>
<td>60.2 ± 11.0</td>
<td>66.8 ± 14.8</td>
</tr>
<tr>
<td>Metastatic intraspinal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>astrocytic tumors</td>
<td>59.3 ± 9.9</td>
<td>48.7 ± 27.5</td>
</tr>
</tbody>
</table>

*Statistically significant difference, t=3.1810, df=37, p=0.003.
†Statistically significant difference, t=-2.4284, df=16, p=0.027.
Single histological types of tumors showed sex-related differences with respect to the age at disease onset (Table 3). Neuroepithelial tumors and all primary intracranial tumors occurred in men at significantly older age (p = 0.001 and p = 0.007, respectively) than in women, whereas meningeal tumors occurred in women at older age than in men, but not significantly (p = 0.079). The occurrence of metastatic tumors at significantly older age in men than in women was mostly the result of metastasis of primary lung tumors, with metastasis occurring in only 4 female patients after the seventh decade of life.

Discussion

Our study did not establish a greater incidence of malignant diseases in the Istrian County than in other counties in Croatia over the last few years, as stated in local daily papers (4). The assumption was based on a simplified and unwarranted interpretation of the reports on cancer incidence in Croatia published in Croatian Public Health Bulletins (3). The reports did not provide any specific data on the incidence of malignant diseases, including brain tumors, in the Istrian County than in other parts of Croatia (3). However, the calculation of these rates was based on the Croatian population census from 1991 (4,784,265 inhabitants), whereas the census from 2001 clearly showed a decrease in the number of inhabitants to 4,437,460. Consequently, use of the former census in the calculation of these rates, especially for the last decade, generated a semantic error as the denominator was in excess. Furthermore, there was a war in Croatia in 1991-1995 and, since one-third of the country was under occupation (13), that area did not fall under statistical recording, producing a “loss” in the number of potentially new patients, which increased the error in the calculation (14). Finally, according to the Public Health Bulletins (3), along with the increase in malignant tumors in Istria, there was a decrease in malignant tumors in the County of Liška-Senj (which was partially occupied during the war). This corroborates the validity of our interpretation of malignancy incidence (3).

According to official data, the incidence all malignant diseases (coded according to the International Classification of Diseases as ICD-9 140-208, ICD-10 C00-C30) per 100,000 population in Croatia increased from 296.1 in 1988 to 480.7 in 2000. During the same period, the rates of malignant brain tumors (ICD-9 191, ICD-10 C71) increased from 7.2 to 12.8; of malignant tumors of the meninges (ICD-9 192, ICD-10 C70) from 0.4 to 1.4; and of benign brain tumors (ICD-9 225.0 ICD-10 D32.0-D35.2) from 0.1 to 1.3. The rates for all malignant diseases, malignant brain tumors, and malignant tumors of the meninges in Istria and Liška-Senj County were of the same range. No increase was noticed in malignant diseases either in Istria, or in Labin area for malignant brain tumors.

Another reason for this investigation was our observation that the incidence of malignant diseases among the population of the northern part of the Labin area was above the Croatian average for malignant brain tumors and leukemia with related blood disorders (7.5 and 20.6 per 100,000 inhabitants, respectively) over the 1985-1995 decade (15). With the exception of the Valle d’Aosta in Italy (26/100,000) (16), the incidence of primary intracranial tumors in the world varies between 7.1 and 18.6 per 100,000 (17), and that of primary intraspinal tumors between 0.8 and 2.5 per 100,000 (18). The differences between the reports are due to various factors: methodology of data collection, availability and technological level of health care, number of asymptomatic and accidentally detected patients involved in the analysis, and number of histologically confirmed tumors. Despite the small number of tumors included in our study, the investigation was long-term and thorough, and 84.2% of the tumors were confirmed histologically, which all supports the reliability of the results. Over the studied period, the incidence of CNS tumors in the Labin area was high and constant, which does not support the suggestion that the increase was due to the introduction of CT and NMR examinations (19,20). In fact, the introduction of NMR method has affected mainly the number of diagnosed pituitary gland tumors in our study.

The results of investigations of this kind, involving whole populations (16,18,21-23), show that, histologically, the most frequent primary intracranial tumors are gliomas and tumors of the neuroepithelial tissue in general (40-67%), the meninges (9-27%), and the pituitary gland tumors (8-18%). Among intraspinal tumors, on the other hand, the most frequent are tumors of the meninges, followed by nerve or neuroepithelial tissue tumors, mainly ependymomas (18,24-26). Inclusion of other histologically diagnosed tumors insignificantly increases in the tumor incidence at both locations. Contrasting results have been reported from Kumamoto in Japan (27), Rochester in the USA (20), and the Valle d’Aosta in Italy (16), where meningiomas were more frequent than gliomas and other neuroepithelial tumors. In Rochester, three-fourths of the meningiomas were diagnosed accidentally during autopsy. The frequency of meningiomas and gliomas in the Valle d’Aosta was virtually the same – 2.8% of meningiomas were detected on autopsy (16). High incidence of meningioma in Kumamoto could be related to the atomic bomb explosions in Nagasaki and Hiroshima (28). In our study, the only exceptions were slightly higher incidence of pineal gland tumors (in 3 female patients: 2 girls and one woman) and lower incidence of nerve sheath tumors.

The sex-related CNS tumor incidence ranges between 0.9 and 2.6 (29). Primary intracranial tumors, gliomas and neuroepithelial tumors in general, are more frequent in men, whereas tumors of the meninges and the pituitary gland are more frequent in women (16,18,20-23,27,30,31). However, in our study, the incidence of tumors of the meninges was higher in men and there was only one single patient with pituitary gland adenoma among men. We can offer no explanation for these observations.

The specific incidence of primary intracranial tumors in both men and women significantly increases with age up to 75 years, where after it decreases
The incidence of meningiomas in our study was high before age 30. In a similar report from Los Angeles, USA (32), the incidence of meningiomas before 35 years of age was lower than 1/100,000 inhabitants, whereas in Norway as many as 96% of meningioma cases were diagnosed after the age of 30 (33). Although the number of meningiomas is too low to allow generalizations, these results do point to a certain cohort effect. With the exception of the three patients born between 1960 and 1981, all other meningioma patients were born between 1937 and 1944.

The limitations of our study were a small sample, wide time-span (a quarter of century), and changes in diagnostic possibilities during the study period. Also, for the most of the patients we were not able to collect any information on their social status, employment, and other data that would allow us to debate about etiological hypothesis.

In conclusion, the results of this study point to the high, temporally stable, incidence in primary CNS tumors in Istria. The applied methodology warrants the reliability of the results. Further investigation in this field is needed in Croatia to support or refute the suggestion of an increasing risk of this disease in Istria.

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References


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