ORIGINAL ARTICLE

A 12-year epidemiologic study on primary spinal cord tumors in Isfahan, Iran

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Background: Although primary spinal cord tumors (PSCTs) comprise a minority of primary central nervous system tumors, they often impose a great deal of morbidity on their victims. Few epidemiologic studies have addressed PSCTs in Iran. **Materials and Methods:** We analyzed the demographic/clinical features of all primary intraspinal tumors (with a specific focus on primary intradural spinal cord tumors) identified between 1992 and 2004 in three of the major related hospitals in Isfahan, Iran. We also tracked the malignant cases until 2012. **Results:** 102 patients with primary intraspinal tumors were found; 82 tumors were Intradural (36 intramedullary and 46 extramedullary) and 20 extradural. The principal intradural histological subtypes were nerve sheath tumor (33%), ependymoma (22%), astrocytoma (16%), and meningioma (15%). 20 (19%) of the tumors were malignant. Local pain (43%) and motor disabilities (36%) were the most common first-presenting symptoms in the patients. Male-to-female ratio was significant only in ependymoma (male:female ratio = 3.6, $P < 0.05$). The mean age in meningioma (57 years, standard error [SE]: 15.7) was significantly higher than other types (one-way ANOVA, $P < 0.05$). **Conclusion:** Our results reflect analogous frequency of distribution for PSCTs compared with most of the previous counterpart studies worldwide. The only notable exception was the comparatively fewer frequency of spinal cord meningioma in our study.

Keywords: Epidemiology, spinal cord neoplasms, survival rate

INTRODUCTION

Primary spinal cord tumors (PSCTs) are typically classified into two major groups: Extradural and intradural. Extradural ones usually arise from adjacent connective tissues. In contrast, intradural tumors originate from neural, glial, or meningial cells in the spinal cord and are subcategorized into intramedullary and extramedullary. PSCTs comprise only 4% of primary central nervous system (CNS) tumors.

Regarding the rarity, little population-based studies are available for them.[1] Most of these studies lack uniform pathologic criteria and rarely include nonmalignant cases.[2] A solid fund of knowledge on the clinical and demographic features of each class of tumor can streamline the process of diagnosis and management, which ultimately improves the prognosis.[3,4]

We conducted this epidemiologic study on primary intraspinal tumors in Isfahan to investigate their frequency, clinical presentations, current management, and outcome.

MATERIALS AND METHODS

Tumor registries of three major health care centers in Isfahan city (Al-Zahra, Kashani, and Sayed-Al-Shohada Hospitals) were explored for PSCT cases diagnosed during the period September 1992 through September 2004. The diagnosis had been established by biopsy subsequent to magnetic resonance imaging (with gadolinium-contrast).

Patient demographic/clinical data (gender, age at onset, presenting symptoms) was collected using patients' file and via phone interviews. The patients were categorized into four age groups: Children (0-19 years), younger adults (20-44 years), older adults (45-64 years), and seniors (≥65 years). Initial symptoms were categorized into four groups: Local pain (neck pain, thoracic back pain, low back pain); muscle weakness (decreased limb force); sensory dysfunction (paresthesia, sensory loss, impaired temperature, and vibration sensation); and referral pain (radicular limb pain, e.g., shoulder pain).

Data on tumor characteristics and treatment modalities was also collected from the surgery/pathology notes in the patient file. The tumor histology groupings are largely consistent with the World Health Organization categories for CNS neoplasms.[5] Moreover, based on

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the tumor site in relation to the thecal sac, tumors were categorized into three classes: Intradural intramedullary, intradural extramedullary, and extradural. The tumors were also classified according to their anatomical location across the spinal canal to cervical, thoracic, lumbar, sacral, and filum terminalis. Malignant cases were contacted to follow the patient situation up until 2012.

The SPSS release 16 (SPSS Science Inc., Chicago, IL, USA) was used for statistical analyses. The associations between categorical variables were assessed using Chi-square test (along with reporting χ^2 values and degree of freedom given in parentheses). Binominal tests (test proportion: 50%) were employed to analyze the goodness-of-fit. One-way ANOVA with post-hoc test was used to compare one continuous variable amongst multiple categorical variables. Using binary logistic regression, the impact of different factors on the rate of malignancy was analyzed. The level of statistical significance was set at $P < 0.05$ (two-tailed) in all statistical analyses. Mean ± standard error (SE) of mean was reported where deemed to facilitate interpretation.

RESULTS

All tumors

102 patients (59 male and 43 female) with primary intraspinal tumors were found. The mean overall age at diagnosis was 40.2 (SE: 1.9). A summary of key findings on all cases in this study is presented in [Table 1]. Patient/tumor features by age groups are summarized in [Table 2]. The data on intradural tumors (intramedullary and extramedullary) are juxtaposed with those on extradural tumors in [Table 3]. Twenty out of 102 (19%) tumors were malignant.

Astrocytoma

All of the 16 astrocytomas (11 male, 6 female) were intramedullary. Eleven tumors were of low-grade (nine pilocytic astrocytoma, two diffuse fibrillary astrocytoma)

Table 1: Characteristics by histology of 102 primary spinal cord tumors diagnosed in 1992-2004 in Isfahan, Iran

	All types (%)	Astrocytoma (%)	Ependymoma (%)	Meningioma (%)	Nerve sheath tumor (%)	Others (%)
Total number (percent in all tumors)	102 (100)	16 (15.6)	23 (22.5)	15 (14.7)	34 (33.3)	14 (13.7)
Male-female rate ratio	1.37 (59/43)	2.2 (11/5)	3.6 (18/5)	0.6 (6/9)	1 (17/17)	1 (7/7)
Mean age (years) (standard error)	40.2 (1.9)	32.7 (5.6)	32.8 (3.5)	57.7 (15.7)	40.4 (2.5)	42 (6.3)
Age group (years)						
Children (0-19)	16 (16)	5 (31)	5 (22)	0	3 (9)	3 (21)
Younger adults (20-44)	47 (46)	7 (44)	13 (56)	4 (27)	19 (56)	4 (29)
Older adults (45-64)	25 (24)	1 (6)	3 (13)	5 (33)	11 (32)	5 (36)
Senior (≥65)	14 (14)	3 (19)	2 (9)	6 (40)	1 (3)	2 (14)
Tumor position						
Intradural intramedullary	36 (35)	16 (100)	20 (87)	0	0	0
Intradural extramedullary	46 (45)	0	3 (13)	14 (93)	29 (85)	0
Extradural	18 (18)	0	0	1 (7)	4 (12)	13 (93)
Mixed intra-extradural	2 (2)	0	0	0	1 (3)	1 (7)
Tumor location within spinal canal						
Cervical	31 (24)	10 (45)	6 (18)	2 (12)	12 (31)	4 (22)
Thoracic	52 (40)	7 (32)	8 (23.5)	13 (76)	12 (31)	9 (50)
Lumbar	30 (24)	5 (23)	7 (20)	2 (12)	13 (33)	3 (17)
Sacral	9 (6)	0	5 (15)	0	2 (5)	2 (11)
Filum terminalis	8 (6)	0	8 (23.5)	0	0	0
Malignant	20/102 (19.6)	5 (31)	1 (4)	0	4 (12)	10 (71)
Primary symptom						
Local pain	44 (43)	7 (44)	11 (48)	4 (26)	15 (44)	7 (50)
Muscle weakness	37 (36)	8 (50)	7 (30)	9 (60)	9 (26)	4 (29)
Sensory dysfunction	12 (12)	0	2 (9)	1 (7)	6 (18)	3 (21)
Radicular pain	9 (9)	1 (6)	3 (13)	1 (7)	4 (12)	0
Treatment modalities						
Surgery alone	54 (52)	4 (25)	12 (52)	14 (93)	22 (65)	1 (7)
Surgery and radiotherapy	30 (30)	6 (37.5)	8 (35)	1 (7)	9 (26)	6 (43)
Surgery and chemotherapy	3 (3)	0	0	0	1 (3)	3 (22)
Radiotherapy alone	9 (9)	3 (19)	2 (9)	0	2 (6)	2 (14)
Radiotherapy and chemotherapy	4 (4)	2 (12.5)	1 (4)	0	0	1 (7)
Surgery, radiotherapy and chemotherapy	2 (2)	1 (6)	0	0	0	1 (7)

Table 2: Primary spinal cord tumor characteristics by age groups in 102 cases in Isfahan, Iran, 1992-2004

	Children (0-19 years) (%)	Younger adults (20-44 years) (%)	Older adults (45-64 years) (%)	Senior (≥65 years) (%)
Number/percent of all	16 (15.7)	47 (46.1)	25 (24.5)	14 (13.7)
Mean age (standard error)	12.3 (1.4)	32.5 (1.1)	55.5 (1.2)	70.7 (1.2)
Male:Female ratio	12/4 (3)	27/20 (1.35)	10/15 (0.66)	10/4 (2.5)
Malignancy rate	4/16 (25)	8/47 (17)	5/25 (20)	3/14 (21)
Tumor position				
Intradural intramedullary	10 (62)	18 (38)	3 (12)	5 (36)
Intradural extramedullary	3 (19)	21 (45)	16 (64)	6 (43)
Extradural	3 (19)	8 (17)	6 (24)	3 (21)

Table 3: Tumor characteristics by anatomical location in 102 primary spinal cord tumors diagnosed in Isfahan, Iran from 1992 to 2004

	Intradural		Extradural (%)
	Intradural intramedullary (%)	Intradural extramedullary (%)	
Total number	36	46	20
Male/female ratio	27/9=3	22/24=0.91	10/10=1
Mean aged (standard error)	32.6 (3.2)	45.2 (2.4)	42.5 (5)
Malignant	6 (16.7)	3 (6.5)	11 (55)
Primary symptoms			
Local pain	16 (44)	18 (39)	10 (50)
Muscle weakness	15 (42)	15 (33)	7 (35)
Sensory dysfunction	2 (6)	7 (15)	3 (15)
Radicular pain	3 (8)	6 (13)	0

and five of high-grade type (two anaplastic astrocytoma, three glioblastoma multiform). Five out of 16 tumors were malignant. Four of the five high-grade cases died within 5 years of diagnosis in the mean interval of 2.3 years from treatment. The mean overall radiation dose was 48.7 gray (Gy) (SE = 0.26), ranging from 24 to 58 Gy, at 1.4 Gy per fraction, in 5 weeks.

Ependymoma

Of 23 spinal cord ependymoma (18 male and 5 female), 13 cases were cellular ependymoma, and eight cases were mixopapillary ependymoma. Transcytic and anaplastic type ependymoma each comprised one tumor. About 90% of tumors were intradural intramedullary [Table 1]. Three of the 23 spinal cord ependymoma (13%) had recurred in the meantime of 4 years (SE = 1.7) from treatment. After 7 years from diagnosis, only one patient had died, who was the only (1/23) malignant case with the diagnosis of anaplastic type ependymoma. The mean interval between symptoms onset and diagnosis was 25.5 months (SE = 6.6).

In the 20 patients who had undergone surgery, total to subtotal resection was the method used for tumor removal in 13 cases and partial resection for the rest. A significantly higher involvement of filum terminalis was seen in ependymomas in comparison to other intradural tumors (Pearson $\chi^2 = 29.8$ (4), $P < 0.005$). Six out of eight tumors in which filum terminalis was invaded were mixopaillary ependymoma. The average radiation dose was 50.9 Gy (SE = 0.80), ranging from 32 to 56 Gy, at 1.8 Gy per fraction.

Meningioma

All 15 cases of meningioma (nine female, six male) were benign. Except one case which was extradural, the others were intradural extramedullary. Surgical resection was the main mean of therapy (total to subtotal removal in 11 cases and partial resection in four patients).

Nerve sheath tumor

With 34 nerve sheath tumors (NST) (17 male and 17 female), NST made up 39% of all intradural tumors in our study. 25 schwanoma, 6 neurofibroma, and 3 malignant peripheral NST were the subtypes reported in biopsy. Four out of 34 cases were malignant, three of which were malignant peripheral NST and the other one was schwanoma. Seven out of 34 cases (20%) had recurred in the mean 4.3 months from treatment (SE = 1.8). Of those 22 who had surgery alone, only one had recurred, compared to six recurrences in the 10 patients with adjuvant radiotherapy. However, this might be attributable to the difference between their surgery results as in the former group almost all 22 subjects had total to subtotal resection, while in the latter group, surgery method was a partial removal in 8 of 10 patients. The average symptom onset-diagnosis time was 27.2 months (SE = 4.5). The mean radiation dose was 49 Gy (SE = 0.29), ranging from 30 to 60 Gy, at about 1.6 Gy in fraction.

Other

In the remaining 14 cases of primary intraspinal tumors, 13 (93%) were pure extradural, including a wide variety of histologies; three plasmacytomas, two lymphomas, two chordoma, two chondromas, one neuroblastoma, one meduloblastoma, one hemangioblastoma, a cavernous hemangioma, and one spinal cord squamous cell carcinoma. Tumors were widely distributed across the spinal canal, with some extending throughout the spine.

DISCUSSION

We evaluated 102 primary spinal cord tumors diagnosed during a 12-year period, in three of the major clinical centers in Isfahan, Iran (Al-Zahra, Kashani, and Sayed-Al-Shohada Hospitals). NSTs (33%) and ependymoma (22%) were the most frequent tumor types [Figure 1], like what was found in Chicago and Croatia.[6,7] Nevertheless, meningioma accounted for 15% of our tumors, contrasting with some other reports where it was one of the most common PSCTs.[6-8] The first presenting symptoms were local pain and muscular weakness, regardless of tumor pathology. This is consistent with the findings of a similar study in Chicago, 2010.[9] Considering the length of each anatomical division, all types of tumors showed an even distribution along the spinal canal ($\chi^2 = 4.1$ (3), $P > 0.05$).

As presented in Table 1, the overall male-to-female rate ratio was 1.37 (binominal test, $P = 0.137$). The only statistically significant difference in the histological type between the genders was found for ependymoma (male:female ratio 3.6; $P = 0.011$). The male:female ratio imbalance was near-to-significant in children (binominal test; test proportion = 0.5, $P = 0.077$) with the predominance of males [Table 2]. The male:female ratio was 27/9 in intradural intramedullary tumors, significantly deferring from what was found in intradural extramedullary and extradural cases (Pearson $\chi^2 = 6.7$ (2), $P = 0.034$ [Table 3]).

The mean age of subjects with meningioma was significantly higher than those with other tumor types (one-way ANOVA; $f = 5.1$, $P = 0.001$). A similar finding emerged from a later study in the US.[6] Both NSTs and ependymoma were more common in "younger adults" (32 in total [68%]) ($P = 0.001$). NST was also the predominant histology in "older adults" (11 [44%]) ($\chi^2 = 11.2$ (4), $P = 0.024$). In children (0-19 years, $n = 20$), however, ependymoma had the most frequency ($n = 7$) followed by astrocytoma ($n = 6$), nearly similar to other studies.[10,11]

Patients with intradural intramedullary tumors had a significantly lower mean age than those with intradural extramedullary and extradural tumors (one-way ANOVA, $P = 0.012$). The intradural intramedullary tumors were more common in children (62%) while the intradural extramedullary tumors revealed a higher frequency in older adults (64%) [Table 2].

Malignant tumors were observed more frequently in extradural compared to intradural tumors (Pearson $\chi^2 = 21$ (2), $P = 0.005$). In the intradural tumors, a higher malignancy rate was observed in astrocytomas compared to other histological subtypes (Pearson $\chi^2 = 9.3$ (3), $P = 0.025$ [Figure 2]). However, when binary logistic regression analysis was made, neither tumor histology nor tumor site did not have significant odds ratio in the predicting of malignancy rate ($P > 0.05$). This might have reached significance in the presence of a larger sample size. Gender, age, primary symptoms, and tumor location within spinal cord, did not show meaningful discrepancies between the malignant and non-malignant groups (Chi-square test, $P > 0.05$). Similar findings were reported in some of the previous studies.[12,13]

Several limitations were confronted in this study. Registries in Iran health institutes are not still fully computerized, which leads to underreporting of cases. Moreover, loss of definite biopsy-based diagnosis and lack of consensus on diagnostic criteria for particular subtypes that may result in misclassification.[14] Furthermore, the low incidence of spinal cord tumors and the referral of many patients from the external provinces to Isfahan prevented us from computing the incidence rate.

Few epidemiologic studies have been done so far with a focus on both malignant and non-malignant primary spinal cord tumors. While previous studies often spared extradural tumors from analyses, we focused on all intradural and extradural primary spinal cord tumors. The descriptive and

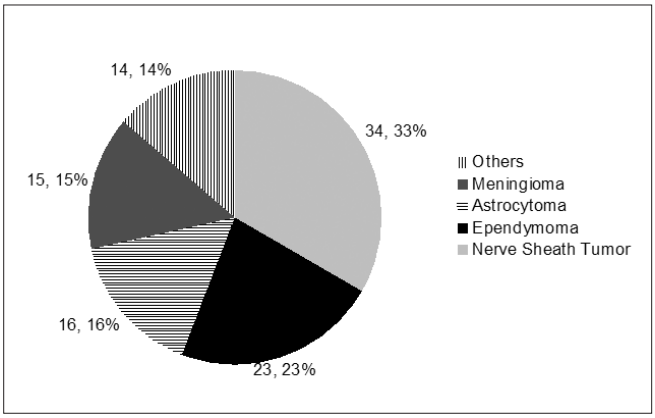

Figure 1: Frequency distribution (number, percent) of primary spinal cord tumors by histological classification in 102 patients: Isfahan, Iran, 1992-2004 (number and percent of cases in each group is noted)

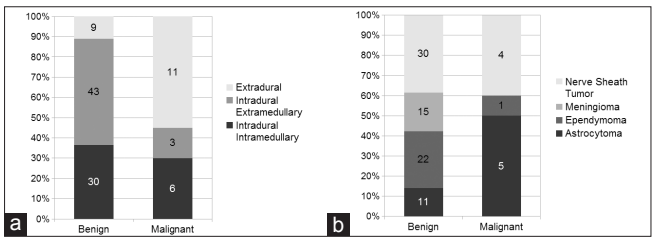

Figure 2: 102 primary spinal cord tumors in Isfahan, Iran, from 1992 to 2004. (a) Tumor location by malignancy in 102 primary spinal cord tumors. Extradural tumors showed a higher tendency toward malignancy than intradural tumors. (b) Tumor histology by malignancy in 88 primary intradural spinal cord tumors. Astrocytomas seemed more likely to be malignant than other types

inferential analyses performed in this study can contribute to the epidemiologic knowledge of PSCTs in Iran.

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