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Original Article

Survival and clinicopathologic characteristics of meningioma

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Abstract. With the prevalence of one-third of intracranial brain tumors, Meningioma prognosis is affected by the size, location, ability to access the tumor through surgery, and the degree of histological malignancy. We intended to investigate patients' prognosis and clinical features with central nervous system meningioma. Records of all patients with central nervous system and spinal cord meningiomas between 2006-2016 in Yazd Shahid Sadoughi, Shahid Rahnemoun, Mortaz, Goodarz, and Mojibian hospitals were studied. Using SPSS version 17, survival, age, type of treatment, grade, size, and tumor location were investigated in this retrospective cross-sectional study. Of the 175 patients (66 (37.7%) male, 109 (62.3%) female) with an average survival time of 78.5 months, tumors recurred in 12 (10.7%) patients. Among them, 63 (47%) were between 18-54, and 72 (53%) were between 55-87 years. Syncytial was the most common histological subtype, and a significant relationship between age and tumor subtype was found (p-value = 0.03). Primary symptoms of headache and nausea/vomiting were in most of them (51, 57%). The most and the most minor expected location was the brain lobes (14 cases) and the spinal cord (2 patients). There was no significant relationship between meningioma subtype-symptoms, survival-gender/ tumor subtype, recurrence-gender/ age, or tumor subtype. Also, a significant relationship between age and survival was found (p-value = 0.05). An increase in the prevalence of meningioma in recent years has been due to improvements in imaging techniques and the population's aging. Overall, there was a significant relationship between age and meningioma prevalence.

Keywords: Meningioma, brain tumor, survival, recurrence

Introduction

Meningiomas are predominantly benign adult tumors, accounting for a third of all intracranial brain tumors [1]. These tumors are often attached to the dura matter and originate from arachnoid meningothelial cells. Meningiomas may develop along any surface outside the brain and inside the ventricular system. They usually present with non-localized and vague symptoms or have local findings related to lower brain tissue compression. Although most meningiomas are separated from the lower brain tissue, some tumors invade the brain, increasing tumor recurrence. The general prognosis of meningiomas is affected by the size, location, ability to access the tumor surgically, and degree of histological malignancy.

Very different histological patterns are found in meningiomas, including syncytial (spiral clusters of compact cells in clusters with no visible cell membranes), fibroblastic (with long cells with abundant collagen between them), transitional (characterized by having syncytial and fibroblastic features), psammomatous (abundant psammoma bodies), secretory (with eosinophilic drops and PAS-positive). NF2 (neurofibromatosis gene) genetic mutations are more common in tumors with a specific growth pattern (fibroblastic, transitional, and psammomatous) [2].

Regarding WHO, meningiomas are classified into four grades, I to IV. So, grade I is benign and contains the most significant amount of total meningiomas, while only 5% of meningiomas are atypical and anaplastic. Unlike grade I meningiomas, which are more common in women, anaplastic and atypical meningiomas are more common in men. Grades II and III are associated with a higher risk of recurrence. Atypical meningiomas are characterized by histological features of prominent nucleoli, increased cellularity, growth without a definite pattern, and a higher mitosis rate, categorized in grades II / IV. Lesions with higher recurrence rates and local growth are more aggressive. Anaplastic meningiomas are highly invasive tumors that resemble sarcomas or carcinomas with a high degree of malignancy. However, there is usually some histological evidence that they originated from meningothelial cells. These are tumors in grades III / IV [3-5].

So far, studies have been performed on meningiomas of the nervous system, which have examined these tumors in terms of epidemiology and clinical features. Most of these

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TABLE 1
FREQUENCY DISTRIBUTION OF TUMOR SUBTYPE BY AGE, GENDER, AND STATUS OF RADIOTHERAPY

Variable		Meningioma types							P
		Syncytial	Transitional	Psammomatous	Atypical	Fibroblastic	Angiomatous	Total	
Gender	Male	18(36.7%)	14(28.6%)	5(10.2%)	6(12.2%)	5(10.2%)	1(2%)	49	**0.82**
	Female	31(34.1%)	28(30.8%)	15(16.5%)	6(6.6%)	9(9.9%)	2(2.2%)	91	
Total		49(35%)	42(30%)	20(14.3%)	12(8.6%)	14(10%)	3(2.1%)	140	
Age	18-54	15(23.8%)	28(44.4%)	8(12.7%)	4(6.3%)	7(11.1%)	1(1.6%)	63	**0.03**
	55-87	32(44.4%)	14(19.4%)	10(13.9%)	8(11.1%)	6(8.3%)	2(2.8%)	72	
Total		47(34.8%)	42(31.1%)	18(13.3%)	12(8.9%)	13(9.6%)	3(2.2%)	135	
Radiotherapy	No	46(35.7%)	37(28.7%)	19(14.7%)	11(8.5%)	13(10.1%)	3(2.3%)	129	-
	Yes	1(25%)	2(50%)	0	1(25%)	0	0	4	
Total		47(35.3%)	39(29.3%)	19(14.3%)	12(9%)	13(9.8%)	3(2.3%)	133	

studies have been conducted in the United States and Europe. These studies have been able to study its prevalence and prognosis in different populations and the pathways involved in the pathogenesis of the disease, factors affecting the course of the disease, and the survival of patients with meningiomas to pathologists [2, 6–12]. In Iran, in some cases, studies have been performed on meningioma and its epidemiological and histopathological factors. However, no reflection on this subject has been published in Yazd so far, and on the other hand, in some of the published articles, the time of publication has been related to the past years [13-19]. Therefore, we decided to study the characteristics of patients with central nervous system meningioma in Yazd from 2006 to 2016 to review the epidemiological, clinical, and pathological findings and prognosis of patients so that in the future and with additional studies, measures can be taken in the control of possible risk factors, diagnosis and treatment steps, and more accurate prognosis of patients.

Materials and Methods

Study design

The present study is a retrospective descriptive-analytical study. The study population included 175 patients with central nervous system, and spinal cord meningioma referred to hospitals in Yazd who underwent neurosurgery from the beginning of 2006 to the end of 2016. The required data were extracted from the archived files of these patients.

In the present study, the required data were collected by referring to the pathology department of all hospitals in Yazd, including Shahid Rahnemoun, Shahid Sadoughi, Mortaz, Goodarz, and Mojibian hospitals. According to the pre-prepared checklist, the required data, including age, sex, clinical symptoms, pathological findings, tumor size, tumor grade, type of treatment performed, and the percentage of recurrence after surgery, were extracted by month and entered into the checklist. The recurrence rate was obtained by referring to patients' files and, if not available, by telephone contact.

Statistical analysis

The obtained data is entered into the software SPSS v. 17 (SPSS, Inc., Chicago, IL, USA). The relationship between the variables was tested using Chi-square and Log Rank statistical tests. The results were recorded in tables and graphs. The significance level was also considered 0.05.

Ethical considerations

According to the Helsinki Convention, patients' information is confidential and was not used anywhere other than the dissertation for research purposes. Permission to view patient records and collect the required data has been obtained from the medical centers. A trained medical student called the patient's family for survival information.

Results

As a cross-sectional analytical study and survival analysis for ten years, this study was performed from 2006 to 2016 in Shahid Sadoughi, Shahid Rahnemoun, Mortaz, Goodarz, and Mojibian hospitals and on 175 patients with meningioma of the central nervous system. Of the 175 patients studied, 66 (37.7%) were male, and 109 (62.3%) were female; the tumor subtype was unknown in 35 patients. Of patients whose recurrence status was known, 12 with meningioma (10.7%) recurred. Six patients with known adjuvant treatment status (3.7 %) underwent radiotherapy. Of the 159 patients whose current life condition was known, five died.

Among 140 patients with known tumor subtypes, 49 (35 %) were male, and 91 (65%) were female. The most common subtypes in both men and women were syncytial (18 men (36.7%) and 31 women (34.1%)). There was no significant difference between meningioma subtypes by gender (p-value = 0.82) (Table 1).

Among 135 patients with known tumor subtypes and age, 63 cases (47 %) were in the age range of 18-54 years, and 72 patients (53%) were in the age range of 55-87 years. The highest frequency among the group of 18-54 years was related to the transitional subtype with 28 cases (44.4%), and then the syncytial with 15 cases (23.8%) had the highest frequency. These findings indicate a significant relationship between the age of meningioma patients and tumor subtypes (p-value = 0.03) (Table 1).

In this study, among 113 patients whose clinical

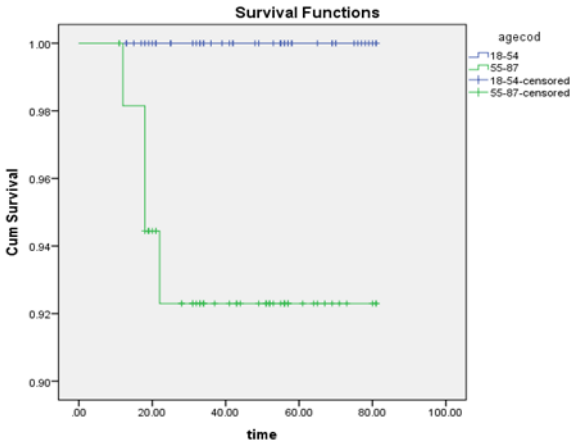

Figure 1 Survival Kaplan-Meier survival curve by the age group in patients with meningioma (log-rank test: 0.05).

symptoms were evaluated, the highest prevalence of symptoms was related to 65 patients (37.1%) who presented with early symptoms of headache and vomiting/ nausea and were diagnosed with meningioma by imaging. Next are 30 patients (17.1%) randomly diagnosed with meningioma in imaging without clinical symptoms. This study has seven cases (4%) with seizures and paralysis. The lowest number of patients was 4 cases (2.3%), belonging to the group of patients with other symptoms such as urinary incontinence.

Among 90 patients whose tumor subtype and clinical manifestations were known, 51 (57 %) with headache and nausea, and vomiting, 25 (27 %) were asymptomatic, 4 (4 %) with seizures, 7 (8) % had presented with paralysis, and three patients (3%) had other symptoms. Among patients with headaches, nausea, and vomiting, the most reported histological subtypes were transitional, syncytial, psammoma, atypical, fibroblastic, and angiomatous. The most common asymptomatic patients were transient, syncytial, psammoma, fibroblastic, and atypical. In patients with seizures, the highest frequency was related to the syncytial form, followed by transitional and fibroblastic. In patients with the initial manifestation of paralysis, syncytial and transitional were the most common. The most common type of tumor diagnosed in patients with miscellaneous symptoms was syncytial. There was no significant relationship between the meningioma subtype and patients' clinical symptoms (p-value> 0.05).

In this study, among 34 patients whose meningioma location was known, most cases were located in the brain lobes (14 cases), and the minor cases were related to the spinal cord (2 cases). It should also be noted that 13 cases (7.4%) had meningioma at the base of the brain, and 5 cases (2.9%) had parasagittal and midline meningioma.

Among 133 patients with known subtype and radiotherapy status, 4 (3%) underwent radiotherapy, of which one was atypical, two were transitional, and one was syncytial subtype (Table 1).

Among the 114 patients who were followed up, the mean survival time in the study was 78.5, with a 95% confidence interval in the range of [76.19-80.90]. The number of patient deaths was 4 cases.

Of the 114 patients who were followed up, 46 were male, and 68 were female. The average survival time of the men was 76.34 months with a 95% confidence interval [71.25-81.43], and the average survival of women was 80 months with a 95% confidence interval [78.5-81.94]. These findings did not show a significant relationship between patients' survival and gender.

Of the 111 patients whose living conditions were known, four patients died, all in the 55-87 age group. The mean survival time in the 55-87 was 79.21 months, while in the group of 18-54 was 80 months. The findings showed that survival time decreased statistically significantly with age (Figure 1).

Out of 92 patients whose meningioma subtype and survival time was identified, three deaths (9.4%) occurred in the meningioma group with the syncytial subtype. The average survival in this group is 79.19 months. Death did not appear in the other groups. There was no statistically significant relationship between the meningioma subtype and survival time. Out of 108 patients with available information about tumor recurrence, 10 (9.3%) experienced recurrence with a mean recurrence time of 74.55 months with a 95% confidence interval in the range of [70.75-78.35].

Out of 108 patients with recurrence information, 46 were male, and 62 were female, of which 10 were four males, and six were female. Also, the average recurrence time in the group of men was 74.90 months with a 95% confidence interval [69.21-80.59], and in the group of women, 74.34 months with a 95% confidence interval in the range [69.28-79.39]. No statistically significant relationship was found between recurrence time and patients' gender (p-value = 0.89)

Of the 105 patients whose recurrence and age data were available, 51 were in the age range of 18-54, and 54 were in the age range of 55-87. Four cases of recurrence were in the age group of 18-54 and 6 cases in the age group of 55-87. In the group of 18-54 years old, the average recurrence time was 75.42 months with a 95% confidence interval of [70.19-80.66], and in the 55-87 age group, the average recurrence time was 73.43 with a 95% confidence interval in the range [67.75-79.12]. Thus, there was no statistically significant relationship between recurrence time and the age of patients (p-value = 0.61).

Among 86 patients whose recurrence information and histological subtype of tumors were known, in the syncytial group, 2 cases (6.9%) with a mean recurrence time of 76.38 months, and in the transitional group, one patient (4.3%) with a mean recurrence time of 77.83 months, in the atypical group 2 cases (18%) with a mean recurrence time of 47.94 months, and in the fibroblastic group 2 cases (22%) with a mean recurrence time of 67 months had experienced a recurrence. No recurrence was seen in the psammomatous and angiomatosis groups. Overall, recurrence occurred earlier in the atypical group than in other groups, possibly due to the malignant nature of this pathological subtype. These findings showed no association between the meningioma subtype and tumor recurrence (p-value = 0.42).

Discussion

Meningiomas are benign tumors found in all parts of the central nervous system, including the brain, spinal cord, and orbit. By WHO definition, meningiomas originate in the arachnoid cells of the leptomeninges. These arachnoid cells have a dual origin of embryonic mesenchyme and the anterior portion of the neural crest. According to this definition, meningiomas are classified into 15 subtypes in 3 grades. The most common category of grade I account for 80-90 % of cases and mainly includes meningothelial, fibroblastic, transitional, angiomatous, and psammomatous subtypes. Grade II comprises 5-15 % of all patients and atypical subtypes, clear cell and choroid. Malignant cases in grade III comprise 1-3 % of all cases. This category includes anaplastic, papillary, and rhabdoid subtypes [20–28].

According to studies in the United States, meningioma is the most common intracranial tumor in adults and accounts for one-third of primary central system tumors. The annual incidence of meningioma in the United States is reported to be 8.3 per 100,000 population. This rate increases with age, so in people over 70, the risk is 3.5 times higher over 70 [23, 29, 30]. Criteria for patients entering databases differ in different studies. So, histological confirmation was not required in the CBTRUS database, unlike the databases used in the extensive survey of Xavi et al. in France. Hence, the age group involved in the French study was 55-64 years, while in the CBTRUS database-based studies, the prevalence of meningioma increases with age [31,32]. Recent studies have shown an increase in the incidence of meningioma in different communities, which may be due to improved quality of imaging techniques or increasing age of communities because this tumor has slow growth and is more common among older age groups [33]. In our study, more meningioma cases were found in older age groups. In addition, there was a significant difference in the frequency of meningioma subtypes in the age groups of 18-54 years and 55-87 years.

The incidence of meningioma in women is 56% higher than in men [31]. Although in the present study, no significant difference was found between meningioma subtypes and gender, 37.7% of patients were men, and 62.3% were women, which is consistent with the findings of previous studies.

In the most extensive study of 13038 meningioma patients in France from 2006 to 2010, the most common clinical manifestation was a headache, seen in one-third of patients, followed by motor and sensory disturbances with 29% and seizures with 24.6% in the following categories. Other manifestations included mental disorders, increased intracranial pressure, and miscellaneous manifestations. Of patients, 9% did not show any symptoms at the time of surgery [32]. These findings are similar to the data from our study in which the most common manifestations were headache, nausea, and vomiting (57.7%), except those asymptomatic cases (26.5%) were the second most common clinical manifestation of patients and seizures, paralysis. Miscellaneous symptoms were in the following categories.

In the study of Kallio et al., The most common sites of meningioma were the parasagittal regions and cerebrum falx, sphenoid ridge, the middle cavity, and cerebral lobes, respectively, and the lowest frequency was related to the posterior cavity [34]. In our study, the highest frequency of meningioma was observed in the cerebral lobes (41.2%), cranial base (382%), midline, parasagittal (14.7%), and spinal cord (5.9%), respectively. Patterson et al., Following a 25 -year follow-up of patients with parasagittal meningioma as one of the most common areas of meningioma, showed that the tumor recurrence rate after 25 years was 47%, which was higher compared with tumors in other areas of the nervous system. This finding may be due to the specific location of the tumor and the ease of growth of tumor tissue in the area. Therefore, they suggested long-term follow-up to evaluate the recurrence rate of tumors in this area. On the other hand, the special location of tumors in this area, due to its proximity to venous sinuses and cerebral veins, deprives the surgeon of the possibility of complete resection of the tumor, so the rate of tumor recurrence is higher than tumors in other places [35].

Factors influencing meningioma recurrence include the extent of tumor resection (based on the Simpson scale), tumor grade, older age, and female gender [29,36,37].

Although treatment protocols for meningioma treatment include surgery, radiotherapy, and chemo-therapy, tumor resection is essential in treating and reducing recurrence. Although complete resection of the tumor is curable to treat cases of benign meningioma, there will still be a small risk of local recurrence, with rates of up to 60% reported over 15 years [38]. However, in studies such as the McCarthy et al. study, which had a shorter follow-up period, a 5 -year recurrence rate of 19.2% was reported for benign meningiomas and 32.4% for malignancies, regardless of the type of treatment [39]. In another 10 -year study by Rogers et al., the recurrence rate was 20-39 % [38]. These differences indicate the need for long-term follow-up to assess the recurrence rate of meningioma in patients. In our study, the overall recurrence rate was 10.7%.

In 2016, a study by Fonkem et al. on 376 meningioma patients showed that the prevalence of meningioma increased with age over 45. Despite the higher prevalence of meningioma in blacks, its majority from 1976 to 2013 is on the rise among whites. In this study, it was shown that there is a significant relationship between age and the frequency of meningioma. Still, due to the lack of a classification of patients with race characteristics or skin color, this relationship was not measured [24].

A study by Das et al. in Singapore found that the most common tumor of the central nervous system was a meningioma, which also showed dysfunction of P53 and apoptotic disorder has not been effective in the pathogenesis of meningiomas [40]. While in a study by Taghipour zahir et al. conducted in Yazd province from 2006 to 2013, the highest prevalence of central nervous system tumors is related to astrocytoma [25]. Tumor pathogenesis was not investigated in our study.

A 2015 study by Harrison et al. investigated the effect of gender on the incidence and prognosis of 1709 cases of spinal cord meningioma, showing that spinal cord meningiomas accounted for a high percentage of spinal cord tumors. Although the prevalence of spinal meningioma is higher in women, the mortality of this tumor is higher in

men [31]. In this study, we had two cases of spinal cord meningioma that did not cause mortality.

In 2007, Rogers et al. studied radiotherapy's role in treating intracranial meningiomas. They concluded that small, asymptomatic, slow-growing meningiomas could be followed up by serial examination and imaging. If indicated for surgery, subtotal resection with radiotherapy helps local control of the tumor and improves survival. For meningiomas that were close to the visual pathways or had a high risk of cerebral edema, the technique fractioned External Beam Radiotherapy was suggested [41]. In this study, six patients underwent radiotherapy after surgery, but surgery and radiotherapy techniques were unavailable. Regarding pathological subtype, one case was atypical, 2 cases were transitional, and one was syncytial.

A study by Ikawa et al., conducted in 2017 in Japan on surgery for the elderly with meningioma, found that postoperative mortality rates increased with age (especially over 65 years). This doubles the importance of deciding on surgical indications for the elderly [42]. A systematic review and meta-analysis by Poon et al. found that elderly patients undergoing meningioma surgery were found to have an overall risk of postoperative complications of 20% for these patients. Before surgery, the risk of complications for the patient was calculated so that a better decision could be made about the patient's surgical indication [43]. In the study of Kuratsu et al., the risk of complications after meningioma surgery was 23.3% in people over 70 years and 3.5% in young people [22]. In our study, there were five deaths, all in old age.

A long-term follow-up study conducted by Rochat et al. in Denmark from 1935 to 1984 followed children who underwent meningioma. They concluded that their prognosis was worse than expected. This was partly due to the lack of advanced imaging techniques in those years and the resulting large tumor size at diagnosis. Pediatric meningiomas can also be associated with mutations in the neurofibromatosis two genes, which makes tumor resection difficult [44]. In our study, the minimum age was 18 years and did not include pediatric meningiomas, which may be due to referrals of pediatric brain tumors to more well-equipped surgical centers.

It is suggested that a database with complete details of patients and comorbidities at the time of surgery be prepared. That information about patient visits after surgery is added to the database. Also, if the patient dies, the cause and its connection with meningioma should be determined as much as possible. Long-term follow-up studies will help find more accurate survival and surgical complications.

Conclusion

The increasing prevalence of meningioma in recent years might be due to improved imaging quality and increasing population age. In previous studies, the majority of meningioma in women was significantly higher. Still, in this study, despite a large number of women with meningioma, no significant difference was found between gender and meningioma subtype. The prevalence of meningioma was statistically significant with age. The findings suggest the need for a longer follow-up study.

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Conflict of interest

The authors declare no conflicts of interest

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