Duration of Symptoms in Brain Tumors: Influencing Factors and Its Value in Predicting Malignant Tumors

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Background: *Although brain tumor is a common neurosurgical condition, diagnosis is generally made after long duration of symptoms. This may have negative impact on treatment outcome.*
Objective: *Study the duration of symptoms of brain tumor, how it is influenced by various factors, and find their value in predicting malignant tumors.*
Material and Method: *The authors retrospectively reviewed 185 patients with pathologically proven brain tumors. Pertinent data including age, types of tumors, locations of tumors, symptoms, and duration of symptoms were analyzed by univariate and multivariate analysis.*
Results: *There were 70 males and 115 females. The mean age at diagnosis was 47.3 years. The average duration of symptoms was 471 days with median of 120 days. On univariate analysis, hormone symptoms ($p = 0.001$), age more than 45 years old ($p = 0.005$), malignant tumor ($p < 0.001$), auditory symptoms ($p = 0.004$), and motor symptoms ($p < 0.001$) had significant influence on duration of symptom. In multivariate analyses, malignant types of tumor, age, and hormonal symptoms were significant. In addition, there was higher risk of malignant brain tumor in patients with duration of symptoms 1 month or less ($p < 0.001$).*
Conclusion: *Certain factors were associated with longer duration of symptoms in brain tumors. This information may lead to early diagnosis of brain tumors. Furthermore, duration of symptoms of 1 month or less was suggestive of malignant brain tumors.*

Keywords: *Duration of symptoms, Brain tumors, Symptomatology, Predictive value*

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In brain tumors, there usually is a time lag between an onset of symptoms and the time when the diagnosis is made, which is defined as duration of symptoms. This duration varies among individuals from days to decades. The vast difference in duration of symptoms of brain tumor has been widely published in the literature[1-15], but the factors influencing this duration is limited. The authors investigate the influence of symptomatology on duration of symptoms in patients harboring brain tumors with intention to improve our understanding on what might delay making diagnosis and how to improve it. The authors also investigate on predictive value of duration of symptoms.

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Material and Method

Population

Medical record of adult patients (age equal or greater than 15 years old) with pathologically proven brain tumor treated at division of neurosurgery, Faculty of Medicine, Chulalongkorn University between January 2005 and December 2006 were reviewed. The pertinent information including age, type of tumor, location of tumor, initial symptoms, chief complaint, and duration of symptoms were analyzed.

Duration of symptoms

Duration of symptoms, as reported by patients, was defined as the duration between the initial symptoms that were attributable to that particular tumor to the time when the diagnosis of "brain tumor" was made, not necessarily the time of the treatment.

To minimize the effect of factors that might have lead to the diagnosis, the authors excluded the

patients with previously treated brain tumors as they were likely to be more vigilant to the recurrent ones and the patients whom the diagnosis were made incidentally by working up for unrelated symptoms (for example, MRI as a part of physical check up, CT scan after head trauma, working up for asymptomatic metastatic brain tumor, and syndromic tumor for instance NFII).

Symptoms of the patients were categorized into visual symptom (*e.g.* decreased visual acuity, blurred vision, decreased visual field), hormone symptoms (*e.g.* galactorrhea, change in body weight or facial appearance, menstruation symptoms, libido etc), motor symptoms (weakness of extremity or cranial nerves), increased intracranial pressure (headache, decreased level of consciousness, vomiting), disequilibrium (*e.g.* dizziness, ataxia, vertigo), and seizure.

Statistical analysis

The authors examined the relationship between various factors and duration of symptoms by univariate and multivariate analyses. Univariate analysis was performed on various potential prognostic factors using Chi-square and Mann-Whitney U test.

Linear regression modeling in a forward stepwise mode was use for multivariate analysis to determine the significance of the independent variables (diagnosis, type of symptom, location, age, malignant tumor) on a dependent variable (duration of symptoms). All statistical analyses were performed using computer software, SPSS, Version 13.0 (SPSS, Inc., Chicago, IL). The results were considered statistically significant for $p < 0.05$.

Results

Patient characteristic

Medical records of 201 patients with the diagnosis of brain tumor were reviewed. After excluding syndromic tumor and incidentally diagnosed tumor, 185 patients information was used for the analysis. The age at diagnosis ranges from 16 to 83 years with mean of 47.3 years and median of 47 years. There are 70 males (37.8%) and 115 female (62.2%).

Tumor characteristic

Tumors located in supratentorial and infratentorial compartment in 132 and 50 cases respectively. The tumors located in both supra- and infratentorial compartment in three cases. The distribution of tumor type is shown in Table 1.

Table 1. Distribution of tumors (n = 185)

Type of tumor	n
Vestibular schwannoma	25
Pituitary tumor	
GH producing	7
ACTH producing	4
Prolactin producing	2
Non functioning	26
Astocytoma	9
Anaplastic astrocytoma	2
Glioblastoma	11
Oligodendroglioma	4
Mixed glioma	3
Meningioma	48
Metastasis	20
Lymphoma	4
Epidermoid	3
Ganglioglioma	1
Germinoma	4
Hemangioma	1
Hemangioblastoma	2
Hemangiopericytoma	1
Gliomatosis cerebri (low grade astrocytoma)	1
Pineal tumor	1
Others	6
Total	185

Duration of symptoms

The average duration of symptoms was 471 days with median of 120 days, and minimum was 0 (the diagnosis is made on the same day as the initial symptoms) and maximum was 7300 days. Mean duration of symptoms of common tumors is displayed in Table 2.

Symptoms and type of tumor

Each type of symptoms has different component of tumors as is summarized in Table 3. Some symptoms were more exclusive to a specific type of tumor, for instance hormonal symptoms and functioning pituitary tumor or auditory symptoms and acoustic tumor while others were more widely distributed, for instance equilibrium symptoms.

Fourty-five percent of the patients with visual symptoms had nonfunctioning pituitary tumor and 26.5% had meningioma. Seventy one percent of auditory symptoms were found in the patients with acoustic tumors. Motor symptoms were found in 31, 24.1, and 17.2% in metastasis, meningioma, and glioblastoma respectively. Tumors causing increased

Table 2. Duration of symptoms of various tumors (days)

Type of tumor	n	Mean	Median	Range
GH producing pituitary	7	2,194	1,460	30-7,300
Vestibular Schwannoma	25	553	270	21-2,555
Astrocytoma	8	235	105	7-730
Anaplastic astrocytoma	2	15	15	0-30
ACTH producing pituitary	4	1,147	730	210-2,920
Glioblastoma multiforme	9	19.3	21	0-30
Meningioma	49	468	135	0-1,825
Metastasis	20	48.5	30	0-270
Oligodendroglioma	8	692	180	0-195
Nonfunctioning pituitary	26	342	135	7-2,190
All tumors	185	471	120	0-7,300

Table 3. Constituent of tumors for each symptom (%)

Symptoms	n	Acoustic	FnPit	AA	Astro	GBM	Mening	Mets	Pitui	Oligo	Misc
Visual	49	4.1	2	0	0	0	26.5	4.1	44.9	2	16.3
Auditory	24	70.8	0	0	0	0	16.7	4.2	0	0	8.3
Motor	29	0	3.4	0	0	17.2	24.1	31	0	3.4	20.7
ICP	54	11.1	3.7	0	5.6	5.6	22.2	11.1	13	5.6	22.2
Seizure	25	0	0	4	20	8	28	20	0	16	4
Equilibrium	27	22.2	0	0	3.7	0	37	14.8	11.1	0	11.1
Hormone	13	0	84.6	7.7	0	0	0	0	7.7	0	0

FnPit = functional pituitary tumor; AA = anaplastic astrocytoma; GBM = glioblastoma multiforme; Mening = meninigoma; Mets = intracranial metastasis; Pitui = pituitary tumor; Oligo = oligodendroglioma; Misc = miscellaneous

intracranial pressure were found in all group of tumor except low-grade glioma. Seizure was frequently found in meningioma (28%), followed by metastasis (20%), astrocytoma (20%), oligodendroglioma (16%), and anaplastic astrocytoma (4%). Neither acoustic tumor nor pituitary tumor produced seizure symptoms. Patients with sense of disequilibrium, 37% had meningioma, 22.2% had acoustic neuroma. Majority of the patients with hormonal symptoms had functioning pituitary tumors.

Factors influencing duration of symptoms

On univariate analysis, hormone symptoms, age more than 45, malignant tumor (anaplastic astrocytoma, glioblastoma, germinoma, metastasis, lymphoma), auditory symptoms, motor symptoms had significant influence on the duration of symptom (Table 4). In multivariate analyses, only malignant tumors ($p = 0.002$), age ($p = 0.028$) and hormonal symptoms ($p < 0.001$) were significant.

Duration of symptoms and malignant brain tumor

Duration of symptoms was arbitrary divided into groups < 1 month, > 1 month < 3 month, > 3 and < 6 months, > 6 months and < 12 months, and more than 12 months. There were 58.9% malignant tumor in the group that the duration of symptoms was 1 month or less ($p < 0.001$; OR 19.1 95% CI (8.1-45.3)). When the diagnosis was made after 1 year, there was no malignant tumor in our data (Table 5).

Discussion

There certainly is a time when brain tumors initially develop and do not cause any appreciable symptoms. In this stage, these tumors may be discovered incidentally by annual physical checkup or investigation for other unrelated conditions. When brain tumors reach certain size they do cause symptoms and generally, there is significant time lapse before the diagnosis is made. As majority of brain tumor is treated primarily surgically, therefore, treating

tumors before they encase cranial nerves, vessels, or invading eloquent areas is certainly beneficial despite that the duration of symptoms are not always directly related to the stage or "resectability" of brain tumors[5,16].

Making early diagnosis of symptomatic brain tumor requires certain flow of actions. First, a patient has to realize that a symptom warrants prompt medical attention and it is not something that they should "wait and see" or attribute it to other benign conditions. Second, a patient has to be able to get medical attention meaning that he or she has to have medical care coverage and physicians they can reach in timely fashion[17,18]. Third, a treating physician has to recognize that this symptom is suggestive of brain tumor not other conditions, for instance, tension headache or sinusitis and obtain appropriate investigation and/or consultation[14,19].

In many instances when history is retrospectively reviewed following the diagnosis of brain tumor, some symptoms have existed long before the diagnosis is made but a patient is unaware that these symptoms are of brain tumor and come to medical attention only after significant delay[20-22]. On the other end of the spectrum, some patients sought medical attention early in the course and significant time has elapsed before the diagnosis is made as symptoms are not recognized by a treating physician.

Table 4. Univariate analysis of various factors

Factor/Symptoms	n	Median DOS (days)	Mean DOS (days)	p-value
Visual				
Present	136	180	490.26	0.075
Absent	49	90	417.28	
Seizure				
Yes	25	60	616	0.116
No	160	120	448	
Hormone				
Yes	13	730	1,668	0.001
No	172	90	380	
Disequilibrium				
Present	27	120	570	0.506
Absent	158	90	454	
Hearing				
Normal	161	90	455	0.004
Abnormal	24	302	577	
Motor				
Normal	156	150	513	<0.001
Abnormal	29	30	240	
ICP				
Increase	54	135	295	0.876
Normal	131	90	544	
Malignant				
Yes	42	25	39	<0.001
No	143	180	597	
Age				
45 or less	88	180	653	0.005
More than 45	97	90	305	

ICP = intracranial pressure

Influencing factors

Association between various factors and duration of symptoms in brain tumor has been studied in the literature. Inskip investigated the duration of symptoms in their series of 489 gliomas (354 high-grade, 135 low-grade), 197 meningiomas, 96 acoustic neuromas, and 799 controls, they found no association between duration of symptoms and level of education or income of the patient[6]. Amadasun analyzed 20 cases of acoustic neuroma; they compared weight of tumor removed by surgery and duration of symptoms. They found no association between these two[23]. Charabi instead found correlation between Ki-67 counts of acoustic neuromas and duration of symptoms. Halperin found tendency of longer duration of medulloblastoma in boys as compare to

Table 5. Number of malignant tumor/non-malignant tumor and duration of symptoms

Duration of symptoms	n	Malignant	Nonmalignant	p-value
1 month	56	33 (58.9%)	23 (41.1%)	<0.001
> 1 to 3 month	35	6 (17.1%)	29 (82.9%)	ns
> 3 to 6 month	24	2 (8.3%)	22 (91.7%)	ns
> 6 to 12 months	22	1 (4.5%)	21 (95.5%)	0.03
> 12 month	48	0 (0%)	48 (100%)	<0.001
Total	185	42 (22.7%)	143 (77.3%)	

girls but that did not reach statistical significant[5]. In the present study of Lowry, 714 patients with primary malignant brain tumor, they found that duration of symptoms was significantly longer in the younger group. They postulated that the index of suspicion of brain tumor was probably lower in younger age group and the younger group probably undergoes medical evaluation less frequently[9].

However, the effect of symptomatology on duration of symptoms has been less well investigated. From symptomatology standpoint, a symptom with sudden onset, rapid progression, and more disabling brings a patient to medical attention sooner than that of insidious onset, slow progression, and non-disabling one[20-22,24-27]. A symptom that is nonspecific or "atypical" tends to go unrecognized by a physician[14,19].

From the present data, duration of symptoms of brain tumor varied widely from instantly diagnosed to decades as also seen in previously published data (Table 6). Motor weakness was associated with shorter duration of symptoms, whereas tumors with hormonal symptoms took longer before being diagnosed. This might suggest that motor symptoms were more concerning or apparent to the patient than hormonal ones. Moreover, majority of tumors causing hormonal symptoms were benign while 46% of motor symptom was comprised of malignant tumors (Table 3). This was in line with data of Crawford et al. In the present study, 30 patients with CNS germ cell tumor, hormonal symptoms had the longest duration of symptom[2]. The present data also showed that auditory symptoms were associated with longer duration of symptoms. These were probably due to slow progression nature of these two symptoms. Other symptoms *i.e.* visual problems, disequilibrium, increased ICP, and seizure had no significant influence on duration of symptoms. This was quite surprising because seizure event should be quite alarming to the patient and quite specific for brain pathology[19]; however, in the present

Table 6. Previous published data on duration of symptoms of brain tumors

	Author	Year	n	Duration of symptoms	
				Mean	Med
Germ cell tumor	Crawford[2]	2003	30	257	135
Lymphoma	Tomlinson[32]	1995	89		56
Supratent malig astrocytoma	Murakami[10]	2007	79		
	Rubino[31]	2004	134		
High grade glioma	Inskip[6]	2003	354	57	30
	Steinfeld[12]	1996	204	48.9	28
	Current	2008	13	18.53	21
supratent glioma all grades	Struikmans[13]	1998	46		
Low grade astrocytoma	Fisher[3]	2007	107		
	Current	2008	8	235	105
Low grade glioma	Inskip [6]	2003	135	348	30
Brainstem tumor	Fisher[4]	2000	76		
Metastasis	Christiaans[1]	2002	68		1,185
	Current	2008	20	48.5	30
Oligodendroglioma	Lebrun[7]	2004	32		
Anaplastic oligodendroglioma	Lebrun[7]	2004	49		
Meningioma	Inskip[6]	2003	197	228	60
	Lobato[8]	2004	80	1,059	
	Nakamura[33]	2004	7	609	
	Wong[15]	2002	20	750	
	Current	2008	49	468	135
Acoustic neuromas	Inskip[6]	2003	129	2,664	
	Charabi[34]	1993	94	1,934	
	Current	2008	25	553	270
Overall	Current	2008	185	471	120

report, its relation with duration of symptoms did not reach statistical significance.

The present data could not distinguish between patient versus physician factors on duration of symptoms in brain tumors. For patient, improving public education may bring the patient in sooner or annual medical review of system may allow patients who otherwise would not have come to meet a physician sooner[6]. For physician, suspicion of brain tumor in patient who presents with auditory and hormonal symptoms should be raised.

Predictive value

The present data suggested that brain tumor with short duration of symptoms (< 1 month) was significantly associated with malignant tumor whereas tumors with duration of symptoms 1 year or longer has no risk of malignancy. Other publication investigating predictive value of duration of symptoms also discovered this finding.

Fisher et al studied children with brain stem tumors. They found that longer duration of symptoms (more than 6 months) suggested pilocytic astrocytoma as compare to fibrillary astrocytoma or other glioma and duration of symptoms of greater than 6 months associated with significantly higher percentage of 5 years survival (74% to 36%)[4]. In children with medulloblastoma, disease stage was correlated inversely with duration of symptoms[5]. Struikman found that a short pretherapeutic duration of symptoms was found to be associated with an increased risk of local progressive disease in their series of 49 gliomas[13]. Result from other series of brain tumors also concurred that shorter duration of symptoms predicts shorter survival or a more malignant type of the disease[1,28-31].

Conclusion

Duration of symptoms in brain tumor is influenced by number of factors. Symptomatology, particularly hormonal and auditory symptoms, are symptoms with limited data in the literature despite the fact that they are the symptoms that bring patients to physician and they are the initial data upon which physicians rely for further actions.

From the present article, duration of symptoms serves two values. First, as a milestone, which the authors would like to shorten with hope to see the patients at the early stage of the brain tumor. Larger scale study may bring more insight on relationship between symptomatology and duration of symptoms. Second, as a predictor of malignant and aggressive nature of brain tumor.

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ปัจจัยที่มีผลต่อระยะเวลาของอาการในผู้ป่วยเนื้องอกสมอง และคุณค่าในการพยากรณ์เนื้องอกสมองชนิดร้ายแรง

กฤษณพันธ์ บุณยะรัตเวช, รุ่งศักดิ์ ศิวานุวัฒน์, ไกรศรี จันทรา, สุรชัย เคารพธรรม

ภูมิหลัง: *แม้ว่าเนื้องอกสมองเป็นโรคที่พบบ่อยในผู้ป่วยประสาทศัลยศาสตร์ ผู้ป่วยมักจะมีอาการมาเป็นระยะเวลานานก่อนที่จะได้รับการวินิจฉัยโรค ซึ่งอาจจะทำให้ผลการรักษาไม่ดี*

วัตถุประสงค์: *เพื่อศึกษาปัจจัยที่มีผลกับระยะเวลาของอาการของเนื้องอกสมอง และประโยชน์ของระยะเวลาของอาการในการพยากรณ์เนื้องอกสมองชนิดร้ายแรง*

วัสดุและวิธีการ: *การศึกษาทำโดยการรวบรวมข้อมูลจากเวชระเบียนของผู้ป่วยเนื้องอกสมอง ที่ได้รับการผ่าตัดและยืนยันด้วยผลทางพยาธิวิทยา จำนวน 185 ราย ข้อมูลสำคัญที่รวบรวมได้แก่ อายุ, ชนิดของเนื้องอก, ตำแหน่ง, อาการ, ระยะเวลาของอาการ ข้อมูลที่ได้นำมาหาความสัมพันธ์ของระยะเวลาของอาการกับปัจจัยต่าง ๆ ด้วยการคำนวณทางสถิติ*

ผลการศึกษา: *ผู้ป่วยเป็นผู้ชายจำนวน 70 คน ผู้หญิง 115 คน อายุเฉลี่ยของผู้ป่วยเท่ากับ 47.3 ปี ค่าเฉลี่ยและค่ามัธฌิมของระยะเวลาของอาการเท่ากับ 471 วัน และ 120 วัน ตามลำดับ การวิเคราะห์ทางสถิติแบบ univariate พบว่า ปัจจัยที่มีผลต่อระยะเวลาของอาการได้แก่ อาการทางฮอร์โมน ($p = 0.001$), อาการทางการได้ยิน ($p = 0.004$), อาการทางมอเตอร์ ($p < 0.001$), อายุมากกว่า 45 ปี ($p = 0.005$), เนื้องอกชนิดร้ายแรง ($p < 0.001$) ในการวิเคราะห์แบบ multivariate พบว่า ปัจจัยที่มีผลต่อระยะเวลาของอาการได้แก่ อาการทางฮอร์โมน, อายุ และเนื้องอกสมองชนิดร้ายแรง นอกจากนี้ระยะเวลาของอาการที่ไม่เกิน 1 เดือน บ่งถึงความเสี่ยงที่เนื้องอกสมองจะเป็นชนิดร้ายแรง ($p < 0.001$)*

สรุป: *ปัจจัยบางอย่างมีผลเกี่ยวข้องกับระยะเวลาของอาการของผู้ป่วยเนื้องอกสมอง จากข้อมูลนี้อาจนำไปสู่การวินิจฉัยเนื้องอกสมองในระยะเริ่มต้น นอกจากนี้ระยะเวลาของอาการที่ไม่เกิน 1 เดือน บ่งถึงความเสี่ยงที่เนื้องอกสมองจะเป็นชนิดร้ายแรง*