Primary Brain Tumors in Thais: Symptom Experience and Predicting Factors.

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Abstract: This longitudinal repeated-measure study aimed to evaluate the occurrence, severity, and interference of the common symptoms and their predicting factors of Thais with primary brain tumors before, during, and at the end of radiotherapy. One hundred and sixteen adult and older participants were recruited from three hospitals residing in the metropolitan area of Bangkok. The measures used were a demographic and medical record form, the Mini-Mental State Examination and the M.D Anderson Symptom Inventory-Brain Tumor.

Results revealed that the most common symptoms found in various occurrence and severity dimensions were: fatigue, drowsiness, sleep disturbances, difficulty remembering, and change in appearance. Fatigue and sleep disturbance were the most common symptoms occurring and their severity existed from the beginning to end of radiotherapy. The type of radiotherapy predicted the occurrence and the severity of fatigue, sleep disturbance, difficulty remembering, change in appearance, and feeling upset. Tumor laterality predicted the severity of fatigue, difficulty remembering, change in appearance, pain, and feeling upset, whereas, tumor location predicted only the severity of drowsiness, difficulty remembering and visual impairment. Tumor type predicted the severity of most common symptoms. It is recommended that nurses should be aware of these symptoms in order to facilitate patients to obtain smooth transition during radiotherapy. Nurses who work in radiotherapy clinics and in wards with patients with brain tumours receiving this treatment, should be trained and encouraged to use the scales to assess patients' symptoms. A nursing practice guideline needs to be developed to care for patients receiving radiotherapy, emphasizing symptom assessment and management, and follow up care as well as evaluating patients' clinical outcomes.

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Introduction

Patients with primary brain tumors (PBTs) are faced with physical, emotional, and cognitive symptoms.[1, 2] These symptoms vary according to different factors such as patients' age, gender, prognosis, type and location of tumor and treatment responses.[1-3] In particular, after receiving radiotherapy (RT), including intensity-modulated radiotherapy (IMRT), X-Knife,

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and CyberKnife as the initial treatment or after surgical resection[3], patients usually suffer more with various symptoms. The symptoms can occur in the early or late phase after receiving RT. Early symptoms include nausea, vomiting, dizziness, or headache. The severity of symptoms depended on treatment location, target volume, tumor factors, and radiation techniques.[4] Thus, persons with PBT experience symptoms from both the disease itself and from RT. Many of them can not resume their previous work and roles due to deterioration of physical functions, cognitive functions and social functions. These may eventually affect their quality of life and disrupt the continuity of treatment that would decrease the chance of control of the tumor growth. In order to control or minimize the symptom experiences, it is necessary to understand their occurrence and pattern of change over time as well as predicting factors from the beginning through the end of RT. However, most studies from the USA and European countries have focused on the late side effects of RT[5, 6] at one point in time, and no prospective studies in regard to acute effects on patients with PBTs can be located.[7] In Thailand, there are no reports of studies concerning the common symptoms of patients with PBTs receiving RT so scientific knowledge to support best practice in this group of patients is very limited. Thus, a study to explore patients' symptom experiences, symptom response and how it may change over time was warranted.

Conceptual Framework and Review of Literature

The Symptom Management Model (SMM)[8] was used as a framework to guide this study. The SMM is based on the interrelation of three concepts: symptom experience, management strategies, and outcomes. Symptom experience refers to the subjective experience of a person who interprets changes in bio-psychosocial function, sensation or cognitive function.[9] Symptom experience consists of one's perception of a symptom, evaluation of the meaning of a symptom and response to a symptom. Symptom management refers to the actions that begin with judgment of the symptom experience from the individual's perspective in order to prevent or delay a negative outcome or minimize the symptom experience. Symptom outcomes are the consequences of symptom experiences and symptom management strategies, including functional status, emotional status, self-care, cost, quality of life, morbidity, and mortality.[8, 9] These concepts are framed within the person, health/illness, and environmental dimensions of nursing science. However, this study focused only on symptom experience and its influencing factors which fall into the dimension of nursing science.

Symptoms may be a result of the characteristics of a tumor, and locations of brain tumors can cause different symptoms. A tumor located in a cavernous sinus may compress the visual pathway leading to visual loss.[10] The brain laterality also be affected with symptoms, for example, a left frontal tumor is related to impaired decision-making in persons with low-grade gliomas (LGG).[11] Several studies have described tumor characteristics as predictors of symptom experience in patients with PBTs.[11, 12]

The current modalities of radiation treatment of benign and malignant brain tumors are stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS).[3] IMRT is an example method of RT, while X-Knife and CyberKnife are the types of radiosurgery. These three methods use a Linear Accelerator, the delivery device of therapeutic X-ray that can give high radiation doses to fit the target point guided by the actual image acquired before treatment.[13] All of these methods are called RT. Even though the types and regimens of RT have been found to be related to symptom experiences, previous studies have explored RT-related symptoms at a late stage after completion

of RT, i.e., 6 months to more than 1 year.[2] None of those studies focused on the early stage effects of RT, which might affect patients' experiences.

Aims and Objectives

This study aimed to explore symptoms in their occurrence and severity dimensions and their pattern of changes, as well as life interference in Thai adults with PBTs before, during, and at the end of RT and their predicting factors. The specific objectives were to:

1. Describe the occurrence and patterns of the most common symptoms in occurrence and severity dimensions throughout the period of RT regimen from the initial phase until the completion of RT, and

2. Determine the extent to which tumor factors (laterality, location, and type) and type of RT predicted the most common symptoms in occurrence, severity dimensions and life interference over time.

Methods

Design:

A longitudinal repeated-measure design was used to obtain data prior, during, and at the end of RT in persons with PBTs.

Sample and Setting:

The sample comprised participants with PBTs who received RT at the outpatient clinics of three tertiary care hospitals in Bangkok, Thailand. Two sites were university hospitals and the other was a cancer institute. The following inclusion criteria were set for sampling selection: diagnosis with PBTs according to the World Health Organization grading system or histological tumor confirmation[5], age above 18 years and receiving primary RT. Exclusion criteria were four-fold: persons with other cancers; having had RT previously; having a severe cognitive impairment; or being unable to pass the Mini-Mental State Examination (MMSE).

The sample size was based on the work of Hedeker et al.[13] who estimated the sample size for a longitudinal repeated-measure research design. The attrition rate was expected to be 10% at two time points. Accordingly, the final sample size required was 113 participants. A total number of 130 adults with PBTs were initially approached. One refused to participate and four had other cancers while five had a history of previous RT. Therefore, 120 participants with PBTs participated in the study. At time 1, after receiving cognitive impairment screening, four participants who had a severe cognitive impairment were excluded yielded the final sample of 116 participants. Throughout the data collection period, which included time 2 and time 3, all 116 participants, passed the MMSE test.

Ethical Considerations:

Ethics approval was obtained from the Research Ethics Committee of Faculty of Medicine Ramathibodi and Siriraj Hospital, Mahidol University, and the National Cancer Institute, Thailand. Each participant received essential information about the purposes, research activities, the utility outcome, and the option to withdraw at any time with no effect on their treatment before signing the consent form. The participants were assured of privacy and confidentiality and a code number was assigned to each questionnaire instead of using their real name.

Instruments:

The Mini-Mental State Examination, developed by Tombaugh and McIntyre[14], was used to screen cognitive status. The Thai version of this test was developed after translation by the Institute of Geriatric Medicine, Ministry of Public Health.[15] The MMSE contains 11 questions grouped into seven categories. Each category represents a different cognitive domain. Scoring of each domain is assigned to: orientation to time (5 points), orientation to place (5 points), registration of three words (3 points), attention and calculation (5 points), recall of three words (3 points), language (8 points), and visual construction (1 point).

Scores range from 0 to 30. The cutoff levels classify the severity of cognitive impairment: score 24-30 = normal, score 18-23 = mild, and score 0-17 = severe.[14] The screening of cognitive status for the 116 participants in this study showed that 100 participants had normal cognitive status while 16 had mild cognitive impairment.

The Demographic and Medical Record Form was developed by the principal investigator. It included the participants' ages, type of PBTs, stage of disease, tumor laterality and location, type of RT, dose/fraction, and total dose of RT.

The MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) was used to measure both neurologic and cancer-related symptoms. This was developed by Armstrong et al.[16] and consists of 22 symptoms and 6 interference items to specify the presence of a particular symptom in the last 24 hours. The following are examples of questions: How severe are your symptom? Your pain at its worst? Your fatigue (tiredness) at its worst? The author received the permission to use the Thai-version of MDASI-BT from the MD Anderson Institute. Symptom occurrence was coded as binary data (0 = no symptom and 1 = had a symptom). In total, a high score denotes the higher occurrence of a symptom. Symptom severity and symptom interference were coded as ordinal data (0 = not present to 10 = as bad as you can imagine). Scoring the severity of each symptom is achieved by summing and averaging. The authors referred to the reference of Armstrong et al.[17] to cluster symptom interference from six interfered items. A higher mean score refers to the higher symptom interference. The Cronbach's alpha from the initial phase to the end of RT for symptom severity was .701 (time 1 or T1), .756 (time 2 or T2), and .763 (time 3 or T3) respectively, whereas the Cronbach's alpha from the initial phase to the end of RT for symptom interference was .776 (T1), .790 (T2), and .794 (T3) respectively.

Data Collection: After informed consent was obtained, participants received explanations about how to answer the questionnaire. Approximately 1 week before starting RT (T1) participants were asked to complete the demographic questionnaire and the test for neurocognitive status (MMSE) and complete a self-report on their symptom experiences (MDASI-BT). After receiving RT 8-10 Gy (T2) and at the completion of RT (T3), the cognitive status of the participants was evaluated and those who had normal or mild cognitive impairment were retained to complete the MDASI-BT.

Data Analysis: Descriptive statistics were used to analyze the participants' characteristics, the most common symptoms, and life interference. A line graph was created to evaluate the pattern of symptoms in which time is assumed as categorical variables. The generalized estimating equation (GEE) was used to examine the factors predicting symptoms in the severity and symptom interference, while the logistic GEE was used to evaluate the occurrence (binary scale). Before carrying out a GEE analysis, the choice for selection model and correlation structure was based on the smallest value of the scale parameter and the highest value of a Wald test. Tumor factors (tumor laterality, location, and type) and type of RT were coded as a categorical scale. Time was added to the model as a continuous variable.

Results

Demographics:

The mean age of participants was 48.4 years. The majority presented with meningiomas. Approximately 43.1% of the tumors were situated in the right laterality, while 55.2% of the tumors were located in the middle skull base. Of these, the majority (36.2%) received IMRT with a fractional dose of 1.8- 2.5 Gy up to an accumulated mode dose of 54 Gy. (Table 1).

Table 1 Demographic Characteristics of the Participants (n = 116)

Characteristic	N (%)	Characteristic	N (%)
Age (range 22-78 years)	Mean 48.4		
	SD 10.0		
Type		**Grade**	
Meningiomas	71 (61.2)	WHO I	84 (72.4)
Pituitary adenomas	20 (17.2)	WHO II	14 (12.1)
Schwannoma	14 (12.1)	WHO III	3 (2.6)
HGG	5 (4.3)	WHO IV	4 (3.4)
LGG	4 (3.4)	No pathological report	11 (9.5)
Other tumors	2 (1.7)		
Laterality		**Tumor location/origin**	
Left side	33 (28.4)	Frontal lobe	17 (14.7)
Right side	50 (43.1)	Middle skull base	64 (55.2)
Both sides	11 (9.5)	Posterior skull base	29 (25.0)
Central part	22 (19.0)	Multiple sites	6 (5.2)

Type of RT	N (%)	Dose/fraction		Total dose	
		Range	Mode	Range	Mode
IMRT	42 (36.2)	1.8-2.50	2.0	30.50-69.96	54
X-Knife	34 (29.3)	1.8-3.00	1.8	30.00-50.40	45
CyberKnife	40 (34.5)	4.0-6.75	5.0	20.00-33.75	25

The Most Common Symptoms:

The top five symptoms most frequently presented over 50% at 3 time points were: visual impairment, difficulty remembering, feeling upset, drowsiness, pain, fatigue, and sleep disturbance. The top five of the most severe symptoms at 3 time points included visual impairment, feeling upset, difficulty remembering, drowsiness, fatigue, sleep disturbance and change in appearance. Visual impairment was the most occurrence and severity symptom at three time points. The new symptoms occurring during T2 to T3 were fatigue and sleep disturbances. Over 45% of participants reported symptom interference in regard to their walking, work, mood, general activity and enjoyment of life at 3 time points. Relations with other people had the lowest score of symptoms interfered with daily life at three time points.

Patterns of the Most Common Symptoms:

Fatigue and feeling drowsy more frequently occurred from T1 to T2 and less frequently occurred from T2 to T3 (Table 2, 3, Figure 1). In contrast, their severity increased over time (Tables 2 and 3, Figure 1).

Table 2 Change in Most Common Symptom Experience at three time points (n=116)

Variable	Time1	N	%	Time2	N	%	Time3	N	%
Symptom	Vision	88	75.9	Vision	91	78.4	Vision	88	75.9
Occurrence	Upset	65	56.0	Fatigue	83	75.5	Fatigue	80	69.0
	Remember	65	56.0	Drowsy	81	69.8	Remember	77	66.4
	Drowsy	60	52.7	Remember	72	62.1	Drowsy	77	66.4
	Pain	60	51.7	Sleep	70	60.3	Sleep	73	62.9

Table 2 Change in Most Common Symptom Experience at three time points(n=116) (Cont.)

	Time 1	M (SD)	Time 2	M (SD)	Time 3	M (SD)
Symptom Severity	Vision	4.22 (3.08)	Vision	4.39 (3.04)	Vision	4.07 (3.03)
	Upset	2.41 (2.70)	Drowsy	3.04 (2.50)	Appearance	3.52 (3.54)
	Appearance	2.31 (3.07)	Fatigue	2.91 (2.28)	Drowsy	3.24 (2.84)
	Remember	2.22 (2.53)	Sleep	2.72 (2.57)	Fatigue	3.19 (2.72)
	Drowsy	2.17 (2.49)	Remember	2.56 (2.48)	Sleep	3.01 (2.78)
	Time 1	**M (SD)**	**Time 2**	**M (SD)**	**Time 3**	**M (SD)**
Symptom Interfere	Work	3.90 (3.02)	Walking	4.45 (2.89)	Work	4.08 (2.86)
	Walking	3.79 (3.08)	Work	4.03 (2.92)	Mood	3.92 (2.92)
	Mood	3.54 (2.94)	Mood	3.86 (2.59)	Activity	3.75 (2.82)
	Activity	3.36 (2.96)	Activity	3.76 (2.66)	Walking	3.74 (2.99)
	Enjoyment	1.91 (2.58)	Enjoyment	2.32 (2.64)	Enjoyment	2.09 (2.69)
	Relation	1.86 (2.67)	Relation	2.11 (2.78)	Relation	2.09 (2.72)

Table 3 Predictors of Symptom Occurrence and Severity over Time

Variable	Symptom Occurrence			Symptom Severity	
	Coef.	Odds Ratio	CI	Coef.	CI
Fatigue					
Time	0.83 ***	2.29	1.76-2.96	0.93***	0.65-1.21
Type of RT: IMRT					
X-knife	-0.26	0.77	0.33-1.79	-0.31	-0.96-0.34
CyberKnife	-1.18**	0.31	0.13-0.71	-1.30***	-1.93-(-0.67)
Laterality: Left side					
Right side	0.21	1.24	0.59-2.60	-0.41	-0.71-0.42
Both sides	-0.45	0.66	0.19-2.34	-0.29	-1.27-0.69
Central part	-9.92	4.92	8.88e-68-2.73e+58	-3.02**	-5.13-(-0.91)
Location: Frontal lobe					
Middle skull	0.12	1.13	0.34-3.78	0.36	-0.54-4.85
Posterior skull	-0.03	0.97	0.25-3.79	0.33	-0.71-1.37
Multiple sites	0.76	2.15	0.31-14.75	1.03	-0.41-2.46
Type: Meningiomas					
Pituitary	10.29	29423.55	5.31e-59-1.63e+67	2.75*	0.65-4.85
Schwannoma	0.76	2.15	0.65-7.13	0.71	-0.22-1.64
HGG	29.98	1.04e+13	0	2.63***	1.33-3.94
LGG	1.78	5.95	0.45-77.99	1.52*	-0.06-3.00
Other tumors	39.63	1.62e+17	0	4.18***	2.11-6.25

* = p < .05, ** = p < .01, *** = P < .001

Table 3 Predictors of Symptom Occurrence and Severity over Time (Cont.)

Variable	Symptom Occurrence			Symptom Severity	
	Coef.	Odds Ratio	CI	Coef.	CI
Drowsy					
Time	0.35 ***	1.41	1.17-1.71	0.53**	0.21-0.85
Type of RT: IMRT					
X-knife	-0.48	0.62	0.24-1.59	-0.23	-0.98-0.51
CyberKnife	0.12	1.03	0.42-2.79	-0.26	-0.98-0.47
Laterality: Left side					
Right side	0.24	1.27	0.45-2.86	0.41	-0.24-1.06
Both sides	-0.13	0.88	0.22-3.50	0.27	0.86-1.40
Central part	-22.52	1.65e-10	0	-1.90	-4.33-0.53
Location: Frontal lobe					
Middle skull	0.79	2.19	0.59-8.15	1.13*	0.09-2.16
Posterior skull	0.26	1.30	0.30-5.68	0.97	-0.23-2.17
Multiple sites	-0.22	0.80	0.11-5.92	0.06	-1.60-1.71
Type: Meningiomas					
Pituitary	22.62	6.68e+09	0	1.77	-0.64-4.20
Schwannoma	-0.80	0.45	0.12-1.66	-1.06	-2.13-0.01
HGG	1.91	6.78	0.45-103.24	2.42**	0.92-3.93
LGG	0.10	1.11	0.15-8.44	1.24	-0.45-2.93
Other tumors	22.03	3.71e+09	0.	3.27**	0.89-5.66
Sleepy					
Time	0.55 ***	1.73	1.40- 2.12	0.56**	0.23-0.88
Type of RT: IMRT					
X-knife	-0.47	0.63	0.25-1.58	-0.07	-0.84-0.69
CyberKnife	-1.05**	0.35	0.14-0.86	-0.76*	-1.50-(-0.02)
Laterality: Left side					
Right side	0.49	1.63	0.74-3.61	0.54	-0.13-1.20
Both sides	0.39	1.47	0.38-5.75	0.68	-0.47-1.83
Central part	0.20	1.22	0.07-22.51	-0.02	-2.50-2.46
Location: Frontal lobe					
Middle skull	0.78	2.19	.61-7.92	0.81	-0.25-1.87
Posterior skull	0.74	2.10	.49-9.02	0.79	-0.44-2.01
Multiple sites	-0.20	0.82	.11-5.84	-0.44	-2.13-1.25
Type: Meningiomas					
Pituitary	-1.35	0.25	0.01-4.78	-1.36	-3.83-1.12
Schwannoma	-0.72	0.49	0.14-1.74	-1.01	-2.11-0.08
HGG	0.99	2.60	0.32-22.85	1.61*	0.08-3.15
LGG	-1.67	0.18	0.02-1.72	-1.53	-3.26-0.20
Other tumors	-0.71	0.49	0.03-8.57	-0.61	-3.04-1.83

* = P < .05, ** = P < .01, and *** = P < .001

Table 3 Predictors of Symptom Occurrence and Severity over Time (Cont.)

Variable	Symptom Occurrence			Symptom Severity	
	Coef.	Odds Ratio	CI	Coef.	CI
Remember					
Time	0.27**	1.31	1.11-1.54	0.30*	0.01-0.59
Type of RT: IMRT					
X-knife	-0.90	0.41	0.14-1.20	-0.48	-1.16-0.20
CyberKnife	-1.14*	0.31	0.11-0.91	-1.16**	-1.81-(-0.50)
Laterality: Left side					
Right side	0.51	1.66	0.67-4.15	0.36	-0.23-0.95
Both sides	0.03	1.03	0.22-4.79	0.98	-0.05-2.01
Central part	-30.76	4.37e-14	0	-3.20**	-5.41-0.99
Location: Frontal lobe					
Middle skull	0.34	1.41	0.33-5.97	-0.34	-1.28-0.60
Posterior skull	-0.82	0.44	0.09-2.24	-1.68**	-2.77-(-0.59)
Multiple sites	-0.45	0.63	0.07-6.06	-1.50*	-3.00-0.00
Type: Meningiomas					
Pituitary	31.55	5.08e+13	0	3.28**	1.08-5.48
Schwannoma	-0.28	0.76	0.18-3.24	-0.43	-1.40-0.55
HGG	-0.25	0.78	0.09-6.82	0.85	-0.51-2.22
LGG	2.50	12.12	0.06-2538.70	-0.04	-1.58-1.49
Other tumors	15.07	3499547	0	1.64	-0.53-3.81
Appearance					
Time	0.36***	1.43	1.21-1.69	0.60**	0.23-0.98
Type of RT: IMRT					
X-knife	-0.25	0.78	0.29-2.10	-0.22	-1.10-0.67
CyberKnife	-1.33**	0.26	0.10-0.72	-1.86***	-2.72-(-1.01)
Laterality: Left side					
Right side	-0.19	0.82	0.35-1.94	-0.31	-1.07-0.46
Both sides	-1.02	0.36	0.08-1.72	-1.53*	-2.86-(-0.19)
Central part	-30.09	8.57e-14	0	-3.73*	-6.59-(-0.87)
Location: Frontal lobe					
Middle skull	0.74	2.11	0.51- 8.75	0.30	-0.92-(1.52)
Posterior skull	0.92	2.50	0.49-12.83	0.70	-0.71-2.10
Multiple sites	1.76	5.81	0.55-61.27	1.61	-0.34-3.55
Type: Meningiomas					
Pituitary	28.76	3.10e+12	0	2.08	-0.77-4.93
Schwannoma	-0.08	0.92	0.22-3.78	-1.01	-2.27-0.26
HGG	2.00	7.38	0.51-107.46	2.79**	1.03-4.56
LGG	0.14	1.15	0.13-10.04	-0.34	-2.33-1.65
Other tumors	14.80	2689614	0	1.63	-1.18-4.44

* = p < .05, ** = p < .01, *** = P < .001

Table 3 Predictors of Symptom Occurrence and Severity over Time (Cont.)

Variable	Symptom Occurrence			Symptom Severity	
	Coef.	Odds Ratio	CI	Coef.	CI
Vision					
Time	-5.55e-17	1	0.88- 1.14	-0.08	-0.45-0.29
Type of RT: IMRT					
X-knife	0.33	1.39	0.39-4.96	-0.14	-1.01-0.73
CyberKnife	0.11	1.10	0.34-3.61	-0.09	-0.93-0.75
Laterality: Left side					
Right side	0.45	1.58	0.53- 4.70	0.45	-0.31-1.20
Both sides	-0.57	0.57	0.09- 3.50	0.28	-1.03-1.59
Central part	15.07	3507081	0	-2.06	-4.88-0.76
Location: Frontal lobe					
Middle skull	0.18	1.19	0.19- 7.63	1.29*	0.08-2.49
Posterior skull	-1.50	0.22	0.03- 1.60	-0.33	-1.72-1.07
Multiple sites	0.33	1.39	0.07-27.63	0.51	-1.41-2.42
Type: Meningiomas					
Pituitary	-16.00	1.12e-07	0	1.31	-1.50-4.12
Schwannoma	0.24	1.27	0.28-5.69	-0.93	-2.18-0.31
HGG	-1.51	0.22	0.02-2.13	-1.01	-2.76-0.73
LGG	-1.05	0.35	0.03-4.70	-1.12	-3.09-0.84
Other tumors	2.74	15.53	.0008-269122.4	2.97*	0.20-5.74
Pain					
Time	0.08	1.08	0.88-1.31	0.06	-0.21-0.34
Type of RT: IMRT					
X-knife	0.51	1.67	0.71-3.91	1.09**	0.45-1.73
CyberKnife	0.68	1.97	0.85- 4.55	0.71*	0.10-1.33
Laterality: Left side					
Right side	-0.31	0.73	0.34-1.55	-0.39	-0.94-0.17
Both sides	-0.34	0.71	0.19-2.70	-0.40	-1.36-0.57
Central part	0.12	1.12	0.04-33.37	-2.67*	-4.75-(-0.60)
Location: Frontal lobe					
Middle skull	0.03	1.03	0.32-3.36	-0.01	-0.89-0.87
Posterior skull	-0.03	0.97	0.25-3.82	-0.18	-1.20-0.85
Multiple sites	-1.37	0.25	0.03-2.29	-0.58	-1.99-0.83
Type: Meningiomas					
Pituitary	-0.31	0.73	0.02-22.05	1.89	-0.18-3.95
Schwannoma	0.25	1.28	0.37- 4.41	0.62	-0.30-1.53
HGG	0.98	2.61	0.45-15.15	1.32 *	0.04-2.60
LGG	-0.55	0.58	0.08- 4.18	-0.60	-2.04-0.84
Other tumors	39.35	1.23e+17	.	3.64***	1.61-5.68

* = P < .05, ** = P < .01, *** = P < .001

Table 3 Predictors of Symptom Occurrence and Severity over Time (Cont.)

Variable	Symptom Occurrence			Symptom Severity	
	Coef.	Odds Ratio	CI	Coef.	CI
Upset					
Time	-0.09	0.91	0.76- 1.09	-0.08	-0.41-0.24
Type of RT: IMRT					
X-knife	-0.45	0.64	0.25-1.59	0.11	-0.66-0.87
CyberKnife	-1.16*	0.31	0.13-0.77	-1.14**	-1.88-(-.40)
Laterality: Left side					
Right side	-0.33	0.72	0.33-1.57	-0.23	-0.89-0.43
Both sides	-0.84	0.43	0.11-1.68	-0.43	-1.58-0.73
Central part	-0.84	0.43	0.02-7.99	-2.67*	-5.14-(-0.19)
Location: Frontal lobe					
Middle skull	0.40	1.48	0.42-5.21	-0.09	-1.14-0.96
Posterior skull	0.03	1.03	0.24-4.41	-0.12	-1.34-1.10
Multiple sites	0.00	1.00	0.14-7.11	0.04	-1.64-1.72
Type: Meningiomas					
Pituitary	0.07	1.07	0.06-19.55	1.86	-0.60-4.32
Schwannoma	0.71	2.04	0.56- 7.48	0.10	-0.99-1.19
HGG	-0.16	0.85	0.14- 5.14	-0.35	-1.88-1.18
LGG	-0.59	0.55	0.08- 4.04	-0.89	-2.61-0.83
Other tumors	0.95	2.59	0.11-59.67	2.37	-0.05-4.80

* = P < .05, ** = P < .01, and *** = P < .001

Table 4 Predictors of Symptom Interference over Time

Variable	Symptom Interference	
	Coef.	CI
Time	0.11	0.13-0.34
Type of RT: IMRT		
X-knife	-0.03	-0.58-0.52
CyberKnife	-0.54*	-1.07-(-0.01)
Laterality: Left side		
Right side	-0.05	-0.52-0.43
Both sides	0.29	-0.54-1.12
Central part	-2.13*	-3.92-(-0.35)
Location: Frontal lobe		
Middle skull	-0.29	-1.05-0.47
Posterior skull	0.07	-0.81-0.95
Multiple sites	-1.14	-2.35-0.07
Type: Meningiomas		
Pituitary	1.78*	0.01-3.56
Schwannoma	0.49	-0.30-1.27
HGG	1.45*	0.35-2.55
LGG	-2.11**	-3.35-(-0.87)
Other tumors	2.57**	0.82-4.32

* = P < .05, ** = P < .01, and *** = P < .001

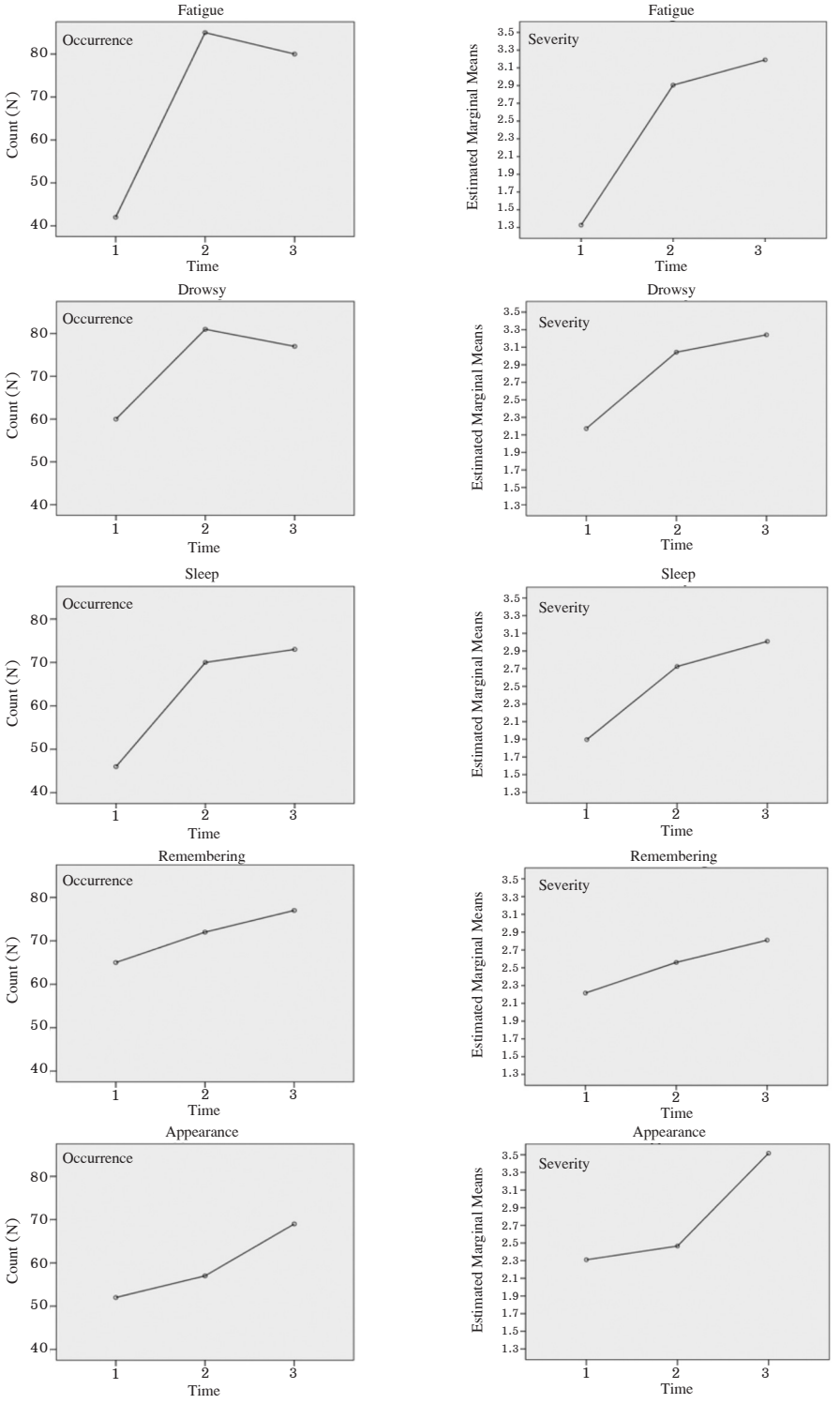

Figure 1 Most Common Symptoms change over Time in Occurrence and Severity Dimensions

Disturbed sleep, problems with remembering, and change in appearance more frequently occurred from baseline to the end of RT (Table 2, 3, Figure 1). Their severity also increased over time (Tables 2, 3, Figure 1).

Factors predicted the Most Common Symptoms:

Type of RT: the occurrence of fatigue, disturbed sleep, difficulty remembering, change in appearance, and feeling upset in participants receiving CyberKnife was less than those receiving IMRT 0.31 times (CI = .13-.71), 0.35 times (CI = .14-.86), 0.31 times (CI = .11-.91), 0.26 times (CI = .10-.72), and 0.31 times (CI = .13-.77), respectively. For the severity dimension, participants receiving CyberKnife reported less severity of fatigue, disturbed sleep, difficulty remembering, change in appearance, and feeling upset than those with IMRT 1.30 times ($p < .001$), 0.76 times ($p < .05$), 1.16 times ($p < .01$), 1.86 times ($p < .001$), 1.14 times ($p < .01$), respectively. Participants receiving CyberKnife and X-knife reported more severe pain than those with IMRT .71 times ($p < 05$) and 1.09 times ($p < .01$), respectively.

Tumor laterality: participants with central area tumor rated severity of fatigue, difficulty remembering, change in appearance, pain, and feeling upset less than those with left side tumor 3.02 times ($p < .01$), 3.20 times ($p < .01$), 3.73 times ($p < .05$), 2.67 times ($p < .05$), and 2.67 times ($p < .05$), respectively. Participants with bilateral tumor rated severity of change in appearance less than those with a left sided tumor 1.53 times ($p < .05$).

Tumor location: participants with a middle skull base tumor felt more severe drowsiness and visual impairment than those with a frontal lobe tumor 1.13 times ($p < .05$) and 1.29 times ($p < .05$), respectively. However, participants with a posterior skull base tumor reported less severe difficulty remembering than those with a frontal lobe tumor 1.68 times ($p < .01$).

Tumor type: participants with a high grade glioma (HGG) had more severe fatigue, feelings of drowsiness, disturbed sleep, changed appearance, and pain than those with a meningioma, 2.63 times ($p < .001$), 2.42 times ($p < .01$), 1.61 times ($p < .05$), 2.79 times ($p < .01$), and 1.32 times ($p < .05$) respectively. Participants with a pituitary tumor had more severe fatigue and difficulty remembering than those with a meningioma, 2.75 times ($p < .05$) and 3.28 times ($p < .01$), respectively. Participants with a pineocytoma or endolymphatic tumor experienced more severe fatigue, feeling drowsy, visual impairment and pain than those with a meningioma, 4.18 times ($p < .001$), 3.27 times ($p < .01$), 2.97 times ($p < .05$) and 3.64 times ($p < .001$), respectively. Participants with a low grade glioma (LGG) experienced more severe fatigue than those with a meningioma, 1.52 times ($p < .05$).

However, the tumor laterality, tumor location, tumor type were not significant in predicting the occurrence of common symptoms over time.

Discussion

Patterns of the Most Common Symptoms:

The most common symptoms in their frequency and severity can be grouped into four separate patterns. First, the frequency of fatigue and feeling drowsy increased from T1 to T2 and decreased from T2 to T3. Second, the severity of fatigue, feeling drowsy, and disturbed sleep increased over time. These two patterns indicated that a number of participants recovered from fatigue and feeling drowsy, whereas others reported fatigue and feeling drowsy more severely, with the highest peak at the end of RT. A possible explanation is that after RT, the blood brain barrier breakdown may occur in the early phase after RT, resulting in frequency and severity of symptoms. Brain edema leads to increased intracranial pressure and makes symptoms worse.[14] Some studies defined the relationship of fatigue, feeling drowsy, and disturbed sleep as an effect of brain radiation in term of somnolence syndrome. This syndrome occurs during

the first phase in the second week of RT and symptoms resolve, then recur again after the fifth week of RT.[15] This is consistent with the study of Powell et al.[16] who reported that patients with PBTs receiving RT experience somnolence at baseline and reached its peak at 6 weeks of RT. The pattern of fatigue and disturbed sleep as well as drowsiness in this study when undergoing RT, is congruent with previous studies in PBTs and other cancers.[17, 18]

The third pattern, the frequency and severity of changes in appearance, increased over time. Our study found that participants changed in their appearance before RT. They experienced facial palsy due to the tumor lesion, skull bone deformity due to surgery, and proptosis or ptosis due to the progression of disease. However, changes in appearance occurred again at the end of RT due to toxicity of radiation, including hair loss and skin erythema. This is similar to a previous study reporting that the most common acute reaction with brain radiation includes hair loss and skin erythema.[19]

The last pattern, the frequency and severity of difficulty in remembering, increased over time. Difficulty in remembering occurred in the early acute phase from the tumor itself and from the side effect of RT. This is consistent with a study of patients with LGG, who reported difficulty remembering in the early phase of RT.[20] However, some previous research found that difficulty in remembering occurred 6 months to 1 year after receiving RT, a late delayed effect.[17]

The frequency and severity of visual impairment, pain, and feeling upset did not change over time in our participants, which is similar to a study in patients with HGG receiving fractionated IMRT.[21] We found that visual impairment was the most frequent symptom with high severity, and this was possibly due to the majority of participants who presented with meningiomas with different lesions that affected the visual pathway. The growth of a visual pathway meningioma can affect visual dysfunction. This finding is consistent with that of Maclean et al.[22] who found that visual deficit was a common clinical problem in patients with meningiomas.

Pain was the most common symptom that occurred at baseline before RT. Similarly Macartney et al. reported that pain was the most common symptom in pediatric brain tumor survivors.[23] In the severity dimension, Armstrong et al.[24] evaluated patients with PBTs and found that pain, fatigue, sleepiness, distress, and difficulty remembering were the most common symptoms presenting in moderate to severe level.

In this study, participants reported that feeling upset was the top of 5 symptoms before receiving RT, possibly due to the complex investigation procedure, the process of preparing for RT, and the suffering from various other symptoms, especially trouble remembering. Consistently Henzel et al.[25] studied people with meningioma and found a high psychological strain before RT, probably due to the primary diagnosis. In our study the participants reported difficulty remembering and this symptom significantly increased over time, while being upset did not significantly change. This result indicates that participants' upset did not contribute to their remembering. Likewise, patients with pituitary adenoma receiving radiosurgery demonstrated that memory loss was not causally related to levels of distress.[26]

Pattern of Symptom Interference:

Symptom interference did not change over time. Work, walking, and mood were ranked as having high interference scores at three time points, while relations with other people was the lowest interference score over time. Likewise Armstrong et al.[27] reported interference scores between 24-hour and 7-day recall period in patients with PBTs, the 24-hour recall similar to 7-day rating. The majority of studies about interference severity conducted with a cross sectional design[28] demonstrate change over time in this dimension limited, and this should be further explored in Thailand.

Factors Predicting the Most Common Symptoms:

The type of RT predicted the most common

symptoms in their occurrence and severity dimensions. Our results indicated that participants receiving CyberKnife showed the occurrence and severity of fatigue, disturbed sleep, difficulty remembering, change in appearance, and feeling upset at a lower level than those receiving IMRT. This indicates that symptom occurrence and symptom severity differed for various types of RT. Fatigue had the most common acute and mildly transient toxicity in persons with meningiomas treated with neither fractionated SRT nor IMRT.[29] The mechanisms of RT-related fatigue and sleep disturbance are unclear, but several studies have supported increased cytokine due to the body using energy to repair normal tissue surrounding the tumor site.[30] In opposition to this, Welzel et al.[31] found that patients treated with radiosurgery demonstrated the strongest decline in memory function. Patients treated with IMRT experienced hair loss and skin irritation more than those who treated with CyberKnife. Hair loss depended on the dose and method of RT. One explanation is that IMRT and Cyberknife effectively beam to target tumor and lessen destroy normal tissue, however CyberKnife is more accurate, using for smaller tumor, and total volume less than those with IMRT. So that areas including hair follicles effect by IMRT more widely than those with CyberKnife.[32] Soldà et al.[33] examined 222 patients with benign intracranial meningiomas receiving stereotactic radiotherapy (type of radiotherapy). The result showed that treatment was associated with mild (rating of severity) transient acute toxicity such as alopecia. There was a limited study comparing the occurrence and severity of disturbed sleep and feeling upset with various types of RT.[4-7] Patients treated with CyberKnife and X-Knife had more severe pain than those who receiving IMRT. Inconsistently, Henzel et al.[25] found that patients with meningioma receiving SRT had a low pain level.

Tumor laterality significantly predicted severity of the most common symptoms over time. Participants with a central brain tumor reported less severe fatigue, difficulty remembering, change in appearance, pain, and feeling upset than those with a left-sided tumor. Participants with a bilateral brain tumor rated their change in appearance less severe than those with left-sided tumor. This indicates that the severity of symptoms might be the result of the tumor laterality. For example, patients with a left-sided tumor demonstrate significantly worse memory function than those with right-sided tumor.[34] This is consistent with Klein[20] who proposed that early neurocognitive dysfunction, including a problem with remembering in patients with LGG, should be attributed to the tumor and/or radiotherapy that occurred in acute phase. However, further studies are needed to confirm this finding because there are very limited studies about this.

Tumor location can also predict the severity of the most common symptoms over time. Participants with a middle skull base tumor reported feeling drowsy and had visual impairment more severely than those with a frontal lobe tumor. This is similar to patients with a middle skull base tumor who also experienced asthenia and drowsiness.[15] Participants with posterior skull base tumor reported difficulty in remembering less severe than those with a frontal lobe tumor. One explanation is that memory function in patients with cerebral tumor decreases due to disturbance of frontal lobe functioning.[35] This result reveals that a frontal lobe tumor seems to have a more severe effect on memory function.

Tumor type can predict the most common symptoms over time. Our results indicated that participants with HGG had more severe fatigue, felt more drowsy, had more disturbed sleep and changes in appearance and pain than those with meningioma. This is similar to patients with HGG treated with IMRT and temozolomide who experienced severe drowsiness after receiving RT 1.5 monthly and had severe pain at baseline to the end of RT.[22] Patients with HGG receiving RT demonstrate dermatological side effects such as dermatitis and alopecia which may take several months to reverse.[36] One explanation

is that patients with HGG always receive high doses of radiation therapy, which may lead to more damage to normal brain tissue, disturbances in sleep pattern,[30] affecting hair loss and skin irritation. Participants with a pituitary tumor in the present study had more severe fatigue and difficulty remembering than those with meningioma, however a previous study found that fatigue was the most common acute toxicity, and was not significantly different between those with meningiomas and pituitary adenoma.[10]

Our participants with pineocytoma or endolymphatic tumor experienced more severe fatigue, visual impairment and pain and felt more drowsy than those with meningioma. Participants with LGG had more severe fatigue than those with meningioma, and the severity of fatigue during RT was found in participants with all types of tumor with the exception of schwannoma. In addition, participants with HGG reported more severe various symptoms than the other tumors. In contrast, LGG affected only fatigue severity.

Factors Predicting Symptom Interference:

Type of RT, tumor laterality, and tumor type predicted symptom interference over time. Our findings demonstrate that patients with LGG had interferences with daily activities at a lower rate than those with meningiomas, while patients with HGG had more interference with daily activities than those with meningiomas. Clinically significant changes were hardly seen as factors affecting symptom interference over time in persons with PBTs. Recent, in a cross-sectional study of Armstrong et al. used symptom interference to predict tumor recurrence and tumor progression in patients with PBTs.[24]

Limitations

In this study, we did not determine cut points for the severity of symptoms to support the severity level because of the limited studies that support cut points for cognitive symptoms in patients with PBTs. In addition, we did not distinguish the severity of symptoms between participants with a recurrent tumor and those with a progressive tumor.

Conclusions and implications for nursing practice

With respect to symptom occurrence and severity dimensions, symptoms significantly worsening over time from the beginning until the end of RT were observed including disturbed sleep, difficulty remembering, and change in appearance. Some symptoms significantly worsening over time in the severity dimension were observed as fatigue and feeling drowsy. However, in the occurrence dimension, fatigue and feeling drowsy decreased from the initial RT to the end of RT. No significant change from baseline to the end of RT were observed in visual impairment, pain and feeling upset. Any alteration of a person's symptoms depends on the type of RT, tumor type, tumor laterality, and tumor location that they have. This finding supports a definitive scope of nursing practice in that in order to facilitate patients obtaining a smooth transition during the early phase of radiation therapy, nurses should be aware of these variables. Patients who have HGG, a left laterality tumor, and who receive IMRT, should be closely monitored throughout the period of radiation therapy. Nurses who work in RT clinics and in wards with patients receiving this radiotherapy for brain cancer should be trained to use the scales to assess patients' symptoms. Nursing leaders are encouraged to work with staff to develop a nursing practice guideline to care for patients receiving RT and implement and evaluate this in clinical practice. This guideline should emphasize symptom assessment, symptom management and follow up care to evaluate patients' clinical outcomes. Further studies should also be conducted to evaluate the effectiveness of the practice guidelines on symptom outcomes.

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เนื้องอกสมองปฐมภูมิในคนไทย: ประสบการณ์การเกิดอาการและปัจจัยทำนาย

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บทคัดย่อ: การศึกษานี้มีวัตถุประสงค์เพื่อสำรวจ อาการแสดงที่เกิดขึ้น ความรุนแรงของอาการ และการรบกวนที่เกิดจากอาการของผู้ป่วยเนื้องอกสมองปฐมภูมิ ใน 3 ช่วงเวลา คือ ตั้งแต่เริ่มให้การรักษาด้วยรังสีระหว่างการรักษา และเมื่อสิ้นสุดการรักษา และศึกษาว่ามีปัจจัยใดบ้างที่ทำนายอาการแสดงที่พบบ่อยตามระยะเวลาที่เปลี่ยนแปลงไป กลุ่มตัวอย่างเป็นผู้ป่วยจำนวน 116 คน ซึ่งมีคุณสมบัติตามเกณฑ์ที่กำหนด และได้รับรังสีรักษาจากโรงพยาบาล 3 แห่งในกรุงเทพมหานคร เครื่องมือที่ใช้ในการวิจัย ประกอบด้วย แบบบันทึกข้อมูลส่วนบุคคล โรค และการรักษา แบบทดสอบสภาพสมองเบื้องต้น และแบบวัดอาการเนื้องอกสมองของนายแพทย์แอนเดอร์สัน

ผลการศึกษาพบว่า อาการแสดงที่เปลี่ยนแปลงทั้งจำนวนการเกิดและความรุนแรงตลอดทั้ง 3 ช่วงเวลาใน 5 อันดับแรก ได้แก่ ความเหนื่อยล้า ความรู้สึกสะลึมสะลือ อาการนอนไม่หลับ อาการหลงลืม และการเปลี่ยนแปลงของภาพลักษณ์ ในขณะที่ความผิดปกติของสายตา ความเจ็บปวด และความรู้สึกไม่สบายใจไม่มีการเปลี่ยนแปลงตลอดทั้ง 3 ช่วงเวลา สำหรับอาการที่พบระหว่างการให้รังสีรักษา คือ ความเหนื่อยล้าและอาการนอนไม่หลับ ชนิดของรังสีรักษา ประเภทเนื้องอกสมอง ซีกสมองด้านที่มีรอยโรค และตำแหน่งเนื้องอกสมอง มีผลต่อจำนวนการเกิดอาการและความรุนแรงของอาการที่เกิดขึ้นกับผู้ป่วย ชนิดของรังสีรักษาเป็นปัจจัยทำนายจำนวนครั้งและความรุนแรงของความรุนแรงของความเหนื่อยล้า การนอนไม่หลับ อาการหลงลืม การเปลี่ยนแปลงของภาพลักษณ์ และความรู้สึกไม่สบายใจ ซีกสมองที่มีรอยโรคมีอิทธิพลต่อความรุนแรงของความเหนื่อยล้า อาการหลงลืม การเปลี่ยนแปลงของภาพลักษณ์ ความปวดและความรู้สึกไม่สบายใจ ตำแหน่งเนื้องอกสมองมีอิทธิพลต่อความรุนแรงของความรู้สึกสะลึมสะลือและอาการหลงลืม ประเภทเนื้องอกสมองเป็นปัจจัยทำนายความรุนแรงของความเหนื่อยล้า ความรู้สึกสะลึมสะลือ อาการนอนไม่หลับ อาการหลงลืม การเปลี่ยนแปลงของภาพลักษณ์ ความผิดปกติของสายตา และความเจ็บปวด จากผลการศึกษาผู้วิจัยมีข้อเสนอแนะว่า พยาบาลควรมีความเข้าใจและตระหนักถึงแบบแผนของอาการที่เกิดขึ้นในผู้ป่วยเนื้องอกสมองปฐมภูมิที่ได้รับการรักษาด้วยรังสีรักษา ตั้งแต่ระยะแรกเมื่อเริ่มรับการรักษาจนสิ้นสุดการรักษา โดยการประเมินอาการและอาการแสดงที่เกิดขึ้นกับผู้ป่วยอย่างต่อเนื่อง ติดตาม เฝ้าระวังและส่งต่ออาการ ตลอดจนพัฒนาแนวทางในการควบคุมและจัดการกับอาการที่เกิดขึ้นอย่างมีประสิทธิภาพ

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