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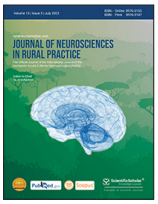

Original Article

Quality of life, out-of-pocket expenditures, and indirect costs among patients with the central nervous system tumors in Thailand

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ABSTRACT

Objectives: The aim of this study was to investigate out-of-pocket (OOP) expenditures, indirect costs, and health-related quality of life (HRQoL) associated with the central nervous system (CNS) tumors in Thailand.

Materials and Methods: A prospective study of CNS tumor patients who underwent first tumor resection at a tertiary care institution in Thailand was conducted. Patients were interviewed during hospitalization for undergoing first surgery. Within 6 months, they were interviewed once more if the disease continued to progress. Costs collected from a patient perspective and converted to 2019 US dollars. For dealing with these skewed data, a generalized linear model was used to investigate the effects of disease severity (malignancy, progressive disease, Karnofsky performance status score, and histology) and other factors on costs (OOP, informal care, productivity loss, and total costs). $P < 0.05$ was considered statistical significant for all analysis.

Results: Among a total of 123 intracranial CNS tumor patients, there were 83 and 40 patients classified into benign and malignant, respectively. In the first brain surgery, there was no statistical difference in HRQoL between patients with benign and malignant tumors ($P = 0.072$). However, patients with progressive disease had lower HRQoL mean scores at pre-operative and progressive disease periods were 0.711 (95% confidence interval [CI]: 0.662–0.760) and 0.261 (95% CI: 0.144–0.378), respectively. Indirect expenditures were the primary cost driver, accounting for 73.81% of annual total costs. The total annual costs accounted for 59.81% of the reported patient's income in malignant tumor patients. The progressive disease was the only factor that was significantly increases in all sorts of costs, including the OOP ($P = 0.001$), the indirect costs ($P = 0.013$), and the total annual costs ($P = 0.001$).

Conclusion: Although there was no statistical difference in HRQoL and costs between patients with benign and malignant tumor, the total costs accounted for more than half of the reported income in malignant tumor patients. The primary cause of significant increases in all costs categories was disease progression.

Keywords: Quality of life, Cost of illness, Health expenditures, Central nervous system, Brain Neoplasms, Neurosurgery

INTRODUCTION

The central nervous system (CNS) tumor is a group of tumors which consist of over 100 histological subtypes and can be broadly divided into two categories (e.g., intracranial and spinal cord tumors).[1] In 2020, the incidence and mortality of brain and other CNS tumors were the highest in Asia (incidence 54.2% and mortality 54.8%), followed by Europe (incidence 21.8% and mortality 8.9%), and North America (incidence 21.4% and mortality 8.8%).[2] Non-malignant brain and other CNS tumors account for the majority of brain and other CNS cancers identified in adult patients, while malignant tumors are relatively uncommon.[3] The treatment outcomes in patients with CNS tumors usually relate to functional deficits which are associated with tumor location, histopathology, the extent of resection, and adjuvant treatment.[4,5] However, symptoms caused by CNS tumors and treatment complications have markedly affected patients' health-related quality of life (HRQoL).[6]

HRQoL is a multidimensional scale for exploring patient's subjective effects of disease and treatment-related symptoms, physical, psychological, and social functioning.[7] Therefore, the change in HRQoL has become one of the most sensitive criterion for investigating cancer treatment outcomes.[8-10] However, there is an insufficient evidence on how HRQoL

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Received: 23 March 2022 **Accepted:** 11 July 2022 **EPub Ahead of Print:** 04 November 2022 **Published:** 16 December 2022 **DOI:** 10.25259/JNRP-2022-3-45

changes with each health status, including pre-operative, and progressive disease in CNS tumors.

Although public health insurance covers most medical expenses for CNS tumors in Thailand, including radiotherapy, chemotherapy, and brain surgery, patients have to pay for other health-care costs such as food, caregiver's wage, and transportation out of pocket. Our knowledge of the costs borne by CNS tumor patients is currently based on limited data. Despite, various studies have examined health-care resource consumption, there is a scarcity of information on the out-of-pocket (OOP) expenditures and indirect costs of early retirement and temporary morbidity.[11-13] Therefore, the primary objective of this study was to assess health utility scores of CNS tumor patients, at pre-operative and progressive disease periods. In addition, the secondary objective was to investigate the OOP expenditures, indirect costs, and annual total costs to better understand the burden of costs experienced by CNS tumor patients in Thailand.

MATERIALS AND METHODS

Data source and target population

A prospective cohort study that consecutively followed patients >18 years of age undergoing first CNS tumor surgery at an 850-bed academic tertiary care hospital in Songkhla Province, Thailand, between September 2018 and August 2019 was conducted. Patients were excluded if they were unable to complete a self-reported questionnaire. All included patients gave their informed consent. The study was approved by the Hospital's Research Ethics Committee.

Disease definition, tumor response, and operational definition

Progressive disease[14] is a condition in which the sum of the diameters of target lesions has increased by at least either 5 mm or 20%, when compared to the smallest mass before therapy. Moreover, the emergence of one or more new lesions is also considered as progression.

An eloquent area is tumor in area that specifically involved motor cortex, sensory cortex, visual center, speech center, basal ganglion, hypothalamus, thalamus, brainstem, and/or dentate nucleus.[15,16] The extent of resection was assessed according to Bloch *et al*.[17]

In all instances, imaging was conducted and evaluated by a neuroradiologist at the pre-operative and post-operative periods. Magnetic resonance images (MRI) of the brain were reviewed to estimate tumor size, tumor location, and other characteristics of the tumor. The post-operative residual tumor was evaluated by post-operative MRI or contrast-enhanced computerized tomography of the brain.

Data collection

Patients were interviewed during hospitalization for undergoing first surgery. Within 6 months, they were interviewed once again if the disease continued to progress. An interview schedule consists of three parts: (1) Demographic information and clinical status, for example, Karnofsky performance status (KPS) and neurologic status, (2) the EuroQol five-Dimensional five-levels (EQ-5D-5L), and (3) costs incurred by patients and family including OOP expenditures, informal care (unpaid caregivers), and productivity loss. Clinical, radiologic, treatment, pathologic data, and pre-operative complications were retrieved from the hospital database.

The HRQoL were collected prospectively using the Thai version of the EQ-5D-5L self-reported questionnaire.[18] According to the Thai value set, the EQ-5D-5L health utility scores were calculated and ranged between −0.283 and 1. The scores "1," "0," and negative values represent the state of perfect health, death, and worse than death, respectively.

The cost analysis was carried out from a patient perspective. All costs were annualized, extracted in Thai currency, and then converted to 2019 United States dollars (in August 2019, 30.65 Baht per dollar).[19] The costs of illness can be divided into three categories: (1) Direct medical expenses, which are typically covered by national public insurance. However, some direct medical costs (i.e., costs of seeking health-care outside patients' public health insurances, which were clinic visits, other medications, and alternative medicines) require patients to pay out of pocket (OOP expenditures); (2) Direct non-medical costs incurred by patients and family, namely, costs for transportation, food, accommodation, home modification, nutrition supplements, and caregiver's salary (OOP expenditures); and (3) Indirect costs include expenditures for informal care (unpaid caregivers) and productivity loss.

Informal care, which is unpaid assistance given by someone with whom they have a social bond, such as a family or other non-kin,[20] was measured using the amount of time that accompanying family members spent on outpatient visits and hospitalizations. Productivity loss is indirect costs incurred with paid and unpaid production loss due to illness, disability, and premature death of productive individuals.[21] Productivity loss estimation was conducted using patient's time spent at the hospital (consultation and hospitalizations) and time unable to work due to CNS tumor. These indirect costs were calculated by multiplying amount of time-loss by patients' individual wage. Daily minimum local wage (320 Thai Baht[22]) was applied to unemployed patients and all family members for estimating productivity loss and informal care.

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics and clinical status. The Chi-squared test was

used to examine categorical variables, but if expected counts were low, the Exact test was utilized instead. For continuous variables (such as age, patient income, and time loss), means and standard deviations were determined. In addition, differences in means were evaluated using independent sample *t*-test. The Shapiro–Wilk test revealed that all costs and most of utility scores were skewed ($P < 0.001$). We expressed costs as mean since other measures (median costs and log transformed costs) are not informative for health policy decisions at the population level.[23] Nonetheless, when making inferences about means for heavily skewed data like costs, a bias-corrected and accelerated non-parametric bootstrap technique was applied to perform the 95% confidence intervals (CI) and *t*-test. Since this method avoids the assumptions of normality that constrain other approaches, it is a more adjustable way of comparing mean costs between groups.[24]

For dealing with these skewed data, a generalized linear model (GLM)[25] was used to investigate the effects of disease severity (malignancy, progressive disease, KPS score, and histology) and costs (OOP, informal care, productivity loss, and total costs). We compared two different distributions (e.g., Gamma and Inverse Gaussian distribution) with either identity or log link function. When the results were presented with identity link, change in mean per unit increase in a covariate was demonstrated. On the other hand, those with log link indicated ratio of means per unit increase in the covariate.[25] The model performance of GLMs were investigated using Akaike Information Criterion (AIC) and graphical analyses.[25-27] Analyses were performed with SPSS software version 22.0.[28] $P < 0.05$ was considered statistical significance.

RESULTS

Baseline characteristics

A total of 131 patients were interviewed between September 2018 and August 2019. On 97 of the 131 cases, total resection was performed, while the remaining 34 received subtotal resection. Eight patients, however, had a spinal cord tumor and were therefore excluded from the analysis. As a result, the data analysis comprised a total of 123 patients with intracranial CNS tumors.

Baseline characteristics are demonstrated in [Table 1]. Mean age was 50.65 years, when categorized by histology, meningioma, glioma, and pituitary adenoma were commonly found in 45 (36.6%), 37 (30.1%), and 15 (12.2%) cases, respectively. In addition, ten of the 15 patients in our study with pituitary adenoma had a functional adenoma, and eight of these ten had visual field defects. Within 6 months after the first brain surgery, 18 patients had disease progression. In addition, 94.4% of these patients had the pre-operative KPS score <80. Average time to disease progression was 4 months. There were 83 and 40 patients classified into benign and malignant tumor, respectively. In addition, the proportion of patients developed to progressive disease and length of hospital stay was significantly worsened ($P < 0.001$) in patients with malignant tumor.

HRQoL

The EQ-5D utility scores categorized by histology and disease severity are shown in [Table 2]. The mean EQ-5D scores at pre-operative and progressive disease periods were 0.711 (95% CI: 0.662–0.760) and 0.261 (95% CI: 0.144–0.378), respectively. All 18 patients with progressive disease were determined to have glioma. In addition, glioblastoma afflicted 11 of these patients. Glioma patients had a low HRQoL of 0.584 (95% CI: 0.487–0.681) before surgery, and their HRQOL worsened to 0.261 (95% CI: 0.144–0.378) as the disease progressed. There was no statistically significant difference between patients having benign and malignant tumor, ($P = 0.072$ at first surgery and $P = 0.557$ at progressive disease).

Costs incurred by patients with CNS tumor

Between benign and malignant tumors, there was no significant difference in any sorts of patient expenditures, including OOP expenditures, indirect costs, and total costs ($P = 0.121$, 0.449, and 0.152, respectively) [Table 3].

The mean annual OOP expenditures in patients with benign tumors were $290.02 (95% CI: $211.54–$368.50, median $180.12), while the mean OOP expenditures were $508.19 (95% CI: $240.68–$775.71, median $187.95) in those with malignant tumors. Since three of the 40 patients with malignant tumor reported a mean cost for caregiver's salary of $2,827.99 (95% CI: $351.59–$5,304.39), the caregiver became the primary cost driver for OOP expenses in patients with malignant tumor. In patients with benign tumors, however, there was no report on costs for caregiver's salary. Food and transportation were the main influences for costs incurred in these patients [Table 3].

The average length of hospital stay was 11.09 and 16.83 days for first brain surgery and progressive disease period, respectively [Table 4]. In addition, the average length of hospital stay was 11.22 and 18.40 days, when patients were classified as having benign and malignant tumors, respectively. The average annual costs of informal care for patients with benign and malignant tumors were $240.29 (95% CI: $167.55–$313.02) and $295.76 (95% CI: $155.80–$435.73), respectively.

Because of the CNS tumor, 79 of the 123 patients were unable to work for an average of 2.05 months. Fifty-six of these 79 patients had benign tumors and had lost an

Table 1: Baseline characteristics and clinical complications in patients with CNS tumor.

Characteristics	Benign (*n*=83)	Malignant (*n*=40)	*P*-value	All patients (*n*=123)
	n (%)	*n* (%)		*n* (%)
Categorical variables				
Gender, *n* (%)				
Male	26 (31.3)	21 (52.5)	0.024	47 (38.2)
Female	57 (68.7)	19 (47.5)		76 (61.8)
Age, year				
Mean (SD)	50.25 (11.73)	51.48 (13.64)	0.609†	50.65 (12.34)
<50	39 (47.0)	17 (42.5)	0.640	56 (45.5)
≥50	44 (53.0)	43 (57.5)		67 (54.5)
Marital status				
Single	16 (19.3)	6 (15.0)	0.263*	22 (17.9)
Married	59 (71.1)	33 (82.5)		92 (74.8)
Other	8 (9.6)	1 (2.5)		9 (7.3)
Education level				
No	2 (2.4)	1 (2.5)	0.197*	3 (2.4)
Primary School	41 (49.4)	18 (45.0)		59 (48.0)
High School	15 (18.1)	14 (35.0)		29 (23.6)
Diploma	9 (10.8)	1 (2.5)		10 (8.1)
University	16 (19.3)	6 (15.0)		22 (17.9)
Occupation				
Farmer and Fisherman	16 (19.3)	17 (42.5)	0.239*	33 (26.8)
Laborer	19 (22.9)	7 (17.5)		26 (21.1)
Merchant/Businessman	14 (16.9)	4 (10.0)		18 (14.6)
Government officer	13 (15.7)	4 (10.0)		17 (13.8)
Unemployment	8 (9.6)	5 (12.5)		13 (10.6)
Householder	9 (10.8)	2 (5.0)		11 (8.9)
Retiree	1 (1.2)	1 (2.5)		2 (1.6)
Private employees	2 (2.4)	-		2 (1.6)
Student	1 (1.2)	-		1 (0.8)
Monthly income, $				
Mean (SD)	418.73 (534.45)	317.33 (437.57)	0.299†	385.76 (505.43)
<$500	63 (75.9)	30 (75.0)	0.605*	93 (75.6)
$500–$999	11 (13.3)	6 (15.0)		17 (13.8)
$1000–$1499	6 (7.2)	1 (2.5)		7 (5.7)
>$1,499	3 (3.6)	3 (7.5)		6 (4.9)
Health insurance				
Universal Coverage Scheme	59 (71.1)	26 (65.0)	0.814*	85 (69.1)
Civil Servant Medical Benefits Scheme	18 (21.7)	11 (27.5)		29 (23.6)
Social Security Scheme	6 (7.2)	3 (7.5)		9 (7.3)
Histology of CNS tumor				
Glioma	7 (8.4)	30 (75)	<0.001*	37 (30.1)
Glioblastoma	-	22 (55.0)		22 (17.9)
Anaplastic astrocytoma	-	7 (17.5)		7 (5.7)
Diffuse astrocytoma	4 (4.8)	-		4 (3.3)
Oligodendroglioma	2 (2.4)	-		2 (1.6)
Anaplastic oligodendroglioma	-	1 (2.5)		1 (0.8)
Ependymoma	1 (1.2)	-		1 (0.8)
Meningioma	45 (54.2)	-		45 (36.6)
Schwannoma	8 (9.6)	-		8 (6.5)
Pituitary adenoma	15 (18.1)	-		15 (12.2)
Brain metastasis	-	10 (25.0)		10 (8.1)
Other brain tumors	8 (9.6)	-		8 (6.5)
Pre-operative clinical status				
Headache	35 (42.2)	26 (65.0)	0.018	61 (49.6)

(Contd...)

Table 1: *(Continued)*.

Characteristics	Benign (*n*=83)	Malignant (*n*=40)	*P*-value	All patients (*n*=123)
	n (%)	*n* (%)		*n* (%)
Motor weakness	20 (24.1)	21 (52.5)	0.002	41 (33.3)
KPS score <80	15 (18.1)	18 (45.0)	0.002	33 (26.8)
Seizure	10 (12.0)	16 (40.0)	<0.001	26 (21.1)
Visual disturbance	24 (28.9)	3 (7.5)	0.007	27 (22.0)
Cranial nerve palsy	8 (9.6)	-	0.053*	8 (6.5)
Progressive disease				
Yes	4 (4.8)	14 (35.0)	<0.001	18 (14.6)
Health-related quality of life				
Preoperative EQ-5D-5L utility scores	0.742 (0.684–0.799)	0.647 (0.553–0.740)	0.072‡	0.711 (0.662–0.760)
Continuous variables	**Mean (SD)**	**Mean (SD)**		**Mean (SD)**
Length of hospital stay, days	12.27 (9.45)	19.75 (13.19)	<0.001	14.70 (11.33)
Time unable to work due to CNS tumor, months	1.22 (1.16)	1.53 (1.78)	0.252	1.32 (1.39)

*Exact test, †*t*-test, ‡*t*-test with bias-corrected and accelerated non-parametric bootstrap technique, *n*=number of total patients

Table 2: EQ-5D-5L utility scores in CNS tumor patients at pre-operative and progressive disease periods, when categorized by histology and disease severity.

Characteristics	EQ-5D-5L utility scores, Mean (95% CI)			
	n	Pre-operative	*n*	Progressive disease
All intracranial tumor	123	0.711 (0.662–0.760)	18	0.261 (0.144–0.378)
Intracranial tumor divided by histology				
Glioma	37	0.584 (0.487–0.681)	18	0.261 (0.144–0.378)
Glioblastoma	22	0.554 (0.414–0.694)	11	0.289* (0.131–0.446)
Other Glioma	15	0.628* (0.488–0.768)	7	0.217 (−0.013–0.446)
Meningioma	45	0.753 (0.676–0.830)	0	NA
Schwannoma	8	0.771 (0.490–1.000)	0	NA
Pituitary adenoma	15	0.859 (0.784–0.935)	0	NA
Brain metastasis	10	0.821* (0.698–0.943)	0	NA
Other brain tumor	8	0.584* (0.327–0.842)	0	NA
Intracranial tumor divided by disease severity				
Benign	83	0.742 (0.684–0.799)	4	0.197* (−0.147–0.541)
Malignant	40	0.647 (0.553–0.740)	14	0.279 (0.137–0.420)
P-value†		0.072		0.557

*Normal distribution by Shapiro–Wilk test, †*t*-test with bias-corrected and accelerated non-parametric bootstrap technique compared between different malignancy status, *n*=Number of total patients, NA=Not available

average of 1.80 months (on average), while the remaining 23 patients had malignant tumors and had lost an average of 2.65 months due to CNS tumors. As a result, productivity loss due to inability to work among patients having benign and malignant tumors was $486.71 (95% CI: $311.74–$661.68) and $507.00 (95% CI: $291.47–$722.53), respectively.

Annual total costs incurred by patients with CNS tumor

Indirect expenditures were the primary cost driver, accounting for 73.81% of total costs borne by CNS tumor patients. In addition, almost half of these indirect costs were productivity loss due to inability to work (35.79% of total cost). The productivity loss due to time spent in the hospital (19.29% of total cost) and informal care (18.74% of total cost) was the second and third cost drivers, respectively.

Costs expressed as a proportion of the patient's annual income

OOP expenditures accounted for 8.27%, 19.12%, and 11.30% of the reported patient's annual income for employed patients with benign tumors (67 of the 83 cases), malignant tumors (26 of the 40 cases), and all patients who reported their income (93 of the 123 cases), respectively.

On the other hand, the disease severity was associated with increases in the proportions of annual indirect costs on the

Table 3: Annual out-of-pocket (OOP) expenditures and annual indirect costs (in 2019 US dollars) incurred by patients with CNS tumor and family members, broken down by disease severity.

Cost categories, Mean (95% CI)	Benign, $			Malignant, $			*P*-value*	All patients, $		
	Patients reporting cost		Total patients (*N*=83)	Patients reporting cost		Total patients (*N*=40)		Patients reporting cost		Total patients (*N*=123)
	n	Costs	Costs	*n*	Costs	Costs		*n*	Costs	Costs
Direct medical costs										
Clinic visits and other medications	0	0	0	0	0	0	N/A	0	0	0
Alternative medicines	0	0	0	1	783.14	19.58 (−20.02–59.18)	0.323	1	783.14	6.37 (−6.24–18.97)
Direct non-medical costs										
Transportation	82	121.50 (95.87–147.13)	120.04 (94.55–145.52)	40	100.83 (73.46–128.20)	100.83 (73.46–128.20)	0.356	122	114.72 (95.45–134.00)	113.79 (94.58–133.00)
Food	83	131.76 (90.57–172.94)	131.76 (90.57–172.94)	40	139.82 (86.46–193.18)	139.82 (86.46–193.18)	0.818	123	134.38 (102.04–166.72)	134.38 (102.04–166.72)
Accommodation	12	63.15 (33.43–92.88)	9.13 (2.98–15.28)	9	38.49 (−5.87–82.84)	8.66 (−1.19–18.51)	0.933	21	52.58 (28.96–76.20)	8.98 (3.82–14.14)
Home modification	1	163.15	1.97 (−1.94–5.88)	3	299.12 (182.11–416.12)	22.43 (−3.31–48.18)	0.120	4	265.13 (140.84–389.41)	8.62 (−0.09–17.33)
Nutrition supplements	2	1,125.76 (−4,471.52–6,723.03)	27.13 (−13.66–67.92)	1	190.89	4.77 (−4.88–14.43)	0.454	3	814.13 (−916.54–2,544.81)	19.86 (−7.71–47.43)
Caregivers' salary	0	0	0	3	2,827.99 (351.59–5,304.39)	212.10 (−39.73–463.93)	0.096	3	2,827.99 (351.59–5,304.39)	68.98 (−12.46–150.41)
Total OOP expenditures	-	-	290.02 (211.54–368.50)	-	-	508.19 (240.68–775.71)	0.121	-	-	360.97 (259.84–462.10)
Informal Care† (Time loss incurred by family members)										
Time spent for outpatient visits and hospitalizations (days)	83	240.29 (167.55–313.02)	240.29 (167.55–313.02)	40	295.76 (155.80–435.73)	295.76 (155.80–435.73)	0.438	123	258.33 (192.39–324.27)	258.33 (192.39–324.27)
Productivity loss† (Time loss incurred by patients)										
Time spent at the hospital for consultation and hospitalizations (days)	83	237.96 (176.29–299.63)	237.96 (176.29–299.63)	40	323.71 (209.18–438.25)	323.71 (209.18–438.25)	0.152	123	265.84 (210.47–321.22)	265.84 (210.47–321.22)
Time for being unable to work due to CNS tumor (months)	56	721.37 (484.10–958.64)	486.71 (311.74–661.68)	23	881.74 588.55–1,174.92)	507.00 (291.47–722.53)	0.890	79	768.06 (582.20–953.92)	493.31 (357.74–628.88)

(*Contd...*)

Table 3: *(Continued).*

Cost categories, Mean (95% CI)	Benign, $			Malignant, $			*P*-value*	All patients, $		
	Patients reporting cost		Total patients (*N*=83)	Patients reporting cost		Total patients (*N*=40)		Patients reporting cost		Total patients (*N*=123)
	n	Costs	Costs	*n*	Costs	Costs		*n*	Costs	Costs
Total indirect costs	-	-	964.95 (727.67–1,202.24)	-	-	1,126.48 (760.13–1,492.82)	0.449	-	-	1,017.48 (820.41–1,214.55)
Total costs from patients' perspective	-	-	1,254.97 (982.25–1,527.69)	-	-	1,634.67 (1,125.82–2,143.53)	0.152	-	-	1,378.45 (1,133.09–1,623.82)

N=Number of total patients, *n*=Number of patients who paid any costs, NA=Not available, The 95% confidence intervals (CI) were calculated using a bias-corrected and accelerated nonparametric bootstrap technique, *t-test with bias-corrected and accelerated non-parametric bootstrap technique, †The indirect costs were calculated by multiplying amount of time-loss by patients' individual wage. Daily minimum wage of Songkhla Province was applied to unemployed patients and all family members for estimating productivity loss and informal care, respectively

Table 4: Time loss in patients with CNS tumor and family members at first brain surgery and progressive disease period.

Time loss	First operation (*N*=123)	Progressive disease (*N*=18)
	n (%)	*n* (%)
Number of accompanying family members		
Mean (SD)	1.53 (0.94)	1.44 (1.04)
Median	1.00	1.00
Minimum - Maximum	1-7	1-5
Length of hospital stay, days		
Mean (SD)	11.09 (8.52)	16.83 (3.99)
Median	8	18
Minimum - Maximum	5-70	9-23
Time unable to work due to CNS tumor, months		
Mean (SD)	1.13 (1.03)	1.41 (1.46)
Median	1	2
Minimum-Maximum	0-3	0-4
Time to progression, months		
Mean (SD)	-	4.00 (1.71)
Median	-	4
Minimum - Maximum	-	1-6

reported patient's annual income. Indirect costs accounted for 40.69% in malignant tumor patients, which was 1.6 times higher than benign tumor patients (25.00%). Similarly, the proportion of total costs incurred by malignant tumors (59.81%) was nearly twice that of benign tumors (33.27%).

The influence of disease severity and baseline characteristics on patient expenditures

[Table 5] demonstrated results of GLM analyses for patient expenditures. GLMs with the inverse Gaussian distribution and the log link were found to be the most applicable models for patient expenditures, according to the AICs and graphical analyses. Gender was not a predictor in any sorts of patients' expenditures, whereas older age (over 50 years old) was a significant predictor of greater OOP expenditures ($P = 0.009$).

When all indicators of disease severity were taken into account, disease progression was found to be significantly associated to rises in all cost categories. Progressive disease was significantly increases in the OOP expenses ($P = 0.001$), the indirect costs ($P = 0.013$), and the total annual costs ($P = 0.001$), with a ratio of mean costs of 3.85 (95% CI: 1.74–8.52), 2.46 (95% CI: 1.21–4.98) and 2.91 (95% CI: 1.51–5.61), respectively, when compared to patients without progressive disease. Although malignant tumors were found to be a significant predictor of decreased OOP expenditures ($P = 0.021$) when compared to benign tumors, no significant difference in total costs was detected. On the other hand, a KPS score was found to have no statistical significance in

Table 5: The impact of disease (malignancy, progressive disease, KPS score, and histology) and other factors on patient expenditures, including out-of-pocket (OOP) expenses, informal care, productivity loss, and total costs.

Characteristics	OOP expenditures		Indirect costs		Total costs	
	*Ratio of mean costs (95% CI)	p-value	*Ratio of mean costs (95% CI)	*P*-value	*Ratio of mean costs (95% CI)	*P*-value
Gender						
Female	1.19 (0.87–1.64)	0.271	0.02 (−0.34–0.38)	0.906	1.06 (0.78–1.45)	0.701
Patients' age, years						
≥50	1.5 (1.11–2.03)	0.009	−0.11 (−0.45–0.22)	0.510	1.01 (0.75–1.35)	0.969
Disease severity						
Malignant	0.61 (0.40–0.93)	0.021	−0.15 (−0.67–0.38)	0.580	0.87 (0.56–1.37)	0.549
Progressive disease	3.85 (1.74–8.52)	0.001	0.9 (0.19–1.61)	0.013	2.91 (1.51–5.61)	0.001
Pre-operative clinical status						
KPS score ≥80	1.03 (0.73–1.46)	0.869	−0.03 (−0.41–0.36)	0.885	0.96 (0.69–1.35)	0.821
Histology						
Glioma	1.81 (1.12–2.91)	0.015	−0.18 (−0.75–0.4)	0.540	0.92 (0.56–1.5)	0.735
Meningioma	1.29 (0.89–1.86)	0.172	−0.36 (−0.77–0.05)	0.086	0.80 (0.56–1.14)	0.216

*Ratios of the mean costs were the exponential of coefficients from the generalized linear model (GLM) with the Inverse Gaussian and log link, References used in each category were gender (male), age group (<50), benign tumor, no disease progression, KPS score <80, not glioma, and not meningioma

predicting costs of any kind. On the other hand, a KPS score < 80 was not a predictor in any costs. Patients with glioma had a significantly higher OOP expenditure (0.015).

DISCUSSION

This study explored the costs suffered by CNS tumor patients in Thailand, addressing a knowledge gap for low- and middle-income countries (LMICs), as prior studies on CNS tumor costs had mostly focused on developed countries. Although this prospective study found no statistical difference in HRQoL and costs between patients with benign and malignant tumors, patients with malignant tumor had significantly higher proportion of patients developing to progressive disease and longer length of hospital stay. We also discovered that the costs spent by malignant tumor patients accounted for over half (59.81%) of the reported income, which was roughly double that of benign tumor patients (33.27%). Among all markers of disease severity, disease progression was the primary factor related to rises in all cost categories. Indirect expenditures were the primary cost driver.

Patients with disease progression had lower HRQoL, compared with newly diagnosed patients, which is in good agreement with the previous findings in high-grade glioma patients.[29] In addition, the previous studies reported that low KPS scores was significantly associated with a poor EQ-5D utility score.[30-32] Similarly, our findings supported such assertions, as we have found that 17 out of total 18 patients with progressive disease had a pre-operative KPS score of < 80, resulting in a low mean utility score of 0.261 (95% CI: 0.144–0.378). Furthermore, the present study revealed that recurrent brain tumor is among the most common cause of increases in all expense categories and longer hospital stays.

Our findings addressed a deficiency in the evidence on OOP expenditures, informal care, indirect costs associated with hospitalization, and indirect costs due to temporary morbidity. We found that the caregiver's salary was the primary cost driver for OOP expenses in patients with malignant tumors. On the other hand, there was no report on the costs of a caregiver's salary in patients with benign tumors. For all patients, the highest non-medical costs were for meals, transportation, and caregivers' salaries. This is consistent with the results of a prior study.[33] In 2006, the financial impact of brain tumors was analyzed in an online survey completed by 277 patients and 224 caregivers in the United States and discovered that meals, transportation, phone bills, housing, and retail goods were the greatest non-medical costs, correspondingly.[33]

Despite the availability of free treatment options in Thailand, CNS tumor patients encountered a financial burden, particularly in malignant tumor patients. In employed patients, the severity of the condition has an impact on their annual income. Patients with benign tumors had a lower ratio of total health expenditure to annual income (n = 67 of 83, mean 33.27%, minimum 4.77%, and maximum 195.81%) than those with malignant tumors (n = 26 of 40, mean 59.81%, minimum 3.88%, and maximum 240.20%). As a result, when compared to individuals with benign tumors, patients with malignant tumors have a greater financial burden. This lends support to the previous findings from the online survey [33], which showed that 91% of patients with brain tumors were employed before diagnosis, compared to only 33% post-diagnosis. They also found that 48% of respondents reported a drop in their household income.

Indirect expenditures were the primary cost driver, accounting for 73.81% of annual total costs borne by CNS

tumor patients. The present study discovered that 67% and 58% of respondents reported lost productivity due to inability to work in patients with benign and malignant tumors, respectively. In addition, although we found that informal care was not a major source of costs incurred by patients, the prior study reported that 16% of caregivers quit their jobs, and 62% cut back on their hours or took time-off.[33]

However, the present study focused only on patients' perspective, a future prospective study from societal perspective including health-care resource utilization and costs associated with CNS tumor treatment in Thailand context is needed. In addition, a longitudinal measurement of the indirect costs associated with premature death, which was not undertaken in this study is required to conduct comprehensive research for costs of CNS tumor care. In 1996, Blomqvist *et al*. assessed the indirect costs of glioblastoma, considering sick leave, early retirement, and mortality in Swedish population.[34] The study reported that indirect expenditures accounted for the largest portion (74%) of the entire cost of disease ($101,058 per patient). Mortality among individuals under the age of 65 was responsible for 73.1% of the indirect expenditures. Early retirement costed $378.4 million, whereas temporary morbidity costed $15.5 million (19.2% and 7.7% of indirect costs, respectively).

The certain limitations of the present study should be acknowledged. First, patients being unable to complete a self-reported questionnaire were excluded from this present study. Although, this protocol may introduce reporting bias into the study, there were just three patients who were excluded from the study.

Second, the sample size is small given the wide spectrum of CNS tumors. The findings may not be nationally representative since our study participants were from a single university-affiliated tertiary hospital. In addition, due to the short 6-month follow-up period, the low rate of progressive disease in intracranial tumors was observed. As a result, there will be a need for more research that includes a longitudinal measurement of HRQoL.

Third, given the fact that data were collected through patient interviews while hospitalized, OOP expenditures associated with hospitalization but not covered by public health insurances were not included in the analysis. However, these costs are anticipated to be low in Thailand because most medical expenses for CNS malignancies are covered by public health insurance.

Finally, in addition to proxy and doctor-reported, patients are more suitable to appraise their health status. Therefore, HRQoL reported by patient's perspective through the PROMs has been increasingly used in the field.[9,10] However, not all HRQoL measures utilized in brain tumor patients are utility-based instrument. As a result, this study utilized the EQ-5D since it is one of the most preferred ways indicated by numerous guidelines[35,36] for eliciting patients' health utility values and using them in health economic evaluation. Although, the use of the EQ-5D may not cover disease specific conditions, compared with several cancer-specific HRQoL measures (e.g., EORTC QLQ-C30) or disease-specific tools (e.g., QLQ-BN20, FACT-Br), this measurement has been used in the field.[31,32] The future research should examine patients' HRQoL independently on each histologic subtype to encompass disease-specific conditions. Furthermore, additional evaluations of the HRQoL of family members as well as the decline in the HRQoL of CNS tumor patients are needed.

CONCLUSION

Although there was no statistical difference in HRQoL between patients with benign and malignant tumors, our findings addressed a deficiency in the evidence on the OOP expenditures, informal care, indirect costs associated with hospitalization, and indirect costs due to temporary morbidity from LMIC. The costs spent by patients with CNS tumors accounted for more than half of the reported income in malignant tumor patients. Disease progression was the leading cause of considerable increase in all categories of costs incurred by patients with CNS tumors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Tunthanathip T, Sae-Heng S, Oearsakul T, Kaewborisutsakul A, Inkate S, Madteng S, *et al*. Quality of life, out-of-pocket expenditures, and indirect costs among patients with the central nervous system tumors in Thailand. J Neurosci Rural Pract 2022;13:740-9.