Quality of Life and Mortality after Craniotomy for Brain Tumor Removal: A South Korean Nationwide Cohort Study

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Abstract

Purpose

We aimed to investigate the prevalence of quality-of-life deterioration and associated factors in patients who underwent craniotomies for brain tumor removal. Additionally, we examined whether deteriorating quality of life after surgery might affect mortality.

Methods

As a national population-based cohort study, data were extracted from the National Health Insurance Service database of South Korea. Adult patients (≥18 years old) who underwent craniotomy for excision of brain tumors after diagnosis of malignant brain tumor between January 1, 2011, and December 31, 2017, were included in this study.

Results

A total of 4,852 patients were included in the analysis. Among them, 2,273 patients (46.9%) experienced a deterioration in quality of life after surgery. Specifically, 595 (12.3%) lost their jobs, 1,329 (27.4%) experienced decreased income, and 844 (17.4%) patients had newly acquired disabilities. In the multivariable Cox regression model, a lower quality of life was associated with a 1.41-fold higher 2-year all-cause mortality (hazard ratio: 1.41, 95% confidence interval: 1.27–1.57; P<0.001). Specifically, newly acquired disability was associated with 1.80-fold higher 2-year all-cause mortality (hazard ratio: 1.80, 95% confidence interval: 1.59–2.03; P<0.001), while loss of job (P=0.353) and decreased income (P=0.599) were not significantly associated.

Conclusions

At one-year follow-up, approximately half the patients who participated in this study experienced a deterioration in the quality-of-life measures of unemployment, decreased income, and newly acquired disability after craniotomy for excision of brain tumors. Newly acquired disability was associated with increased 2-year all-cause mortality.

Introduction

Primary brain tumors are a rare and important type of central nervous system tumor that can cause significantly high mortality and morbidity in people of all ages.[1] In South Korea, the prevalence of primary brain and central nervous system tumors was reported to be 22.01/100,000 individuals from 2007 to 2016.[2] Globally, the overall prevalence of all brain tumors is reported to be 10.82/100,000 person-years.[3] The prevalence of central nervous system tumors has increased globally from 4.63/100,000 person-years in 1990 to 17.3/100,000 person-years in 2016,[4] with the overall 5-year survival rate among patients with primary brain tumors reported to be below 35%,[5, 6] suggesting that its treatment is still a challenging and significant public health issue.

A multidisciplinary team usually personalizes treatment for patients with primary brain tumor through an approach that considers individual tumor location, type, patient age, and physical condition.[7] For surgical treatment, maximum cytoreduction without incurring neurological deficits has been emphasized to improve both survival outcomes and postoperative quality of life (QOL).[1, 7, 8] After a craniotomy for brain tumor removal, various complications—such as neurological complications—can occur,[9] that are known to affect patients in the long term.[10] As brain tumor surgery can cause subsequent functional impairment,[11] patients may develop newly acquired disabilities or become unemployed after recovery. Brain tumor treatment also carries a high financial cost, which adds an additional financial burden for patients to carry.[12] Bearing these factors in mind, the QOL of patients who undergo craniotomy for brain tumors may deteriorate after surgery and this deterioration might affect their long-term survival. However, to our knowledge, this postoperative worsening of QOL has not been clearly quantified.

Therefore, using a nationwide South Korean cohort database, we aimed to investigate the prevalence of deteriorating QOL and associated factors in patients who underwent a craniotomy for brain tumor removal, focusing specifically on changes in the first year after the brain surgery. Additionally, we examined whether a deterioration in QOL might affect mortality.

Materials And Methods

Study Design and Ethical Considerations

As this was a nationwide, population-based cohort study, we followed the Reporting of Observational Studies in Epidemiology guidelines.[13] The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (approval number: X-2104-679-901), and the National Health Insurance Service (NHIS) approved our study’s data provision protocol (approval number: NHIS-2020-1-306). The need for informed consent was waived by the Institutional Review Board because the data were retrospectively analyzed using anonymized data from the NHIS database.

Data Sources

This study analyzed data gathered from the databases of two organizations: the NHIS and Statistics Korea.

The NHIS is the sole public health insurance service in South Korea. All disease diagnoses must be registered in the NHIS database using the International Statistical Classification of Disease and Related Health Problems, 10th Revision (ICD-10) codes. Registration enables patients to receive financial support for treatment expenses. Additionally, all prescription information regarding drugs and/or procedures must also be registered in the NHIS database. For this study, data regarding demographic information, diagnoses, and other variables were extracted from the NHIS.

As a central government organization, Statistics Korea provides statistical information for national planning and coordination. In South Korea, physicians are required to register a disease diagnosis in the

Statistics Korea database using the ICD-10 codes that are most closely related to the cause of death. The primary causes of death were extracted from the Statistics Korea database for use in this study. Accurate dates and causes of death were collected until December 31, 2019.

Study Participants

We extracted data for all cases that satisfied the following two conditions: 1) disease diagnosis code of C71* (malignant neoplasm of the brain) and 2) procedural codes of craniotomy for excision of brain tumors. Thus, patients with brain tumors who underwent craniotomy for brain tumor excision surgery between January 1, 2011 and December 31, 2017, were included in this study. If eligible patients underwent two or more craniotomies for excision of brain tumor, only data for the first surgery were included. Patients younger than 18 years of age were excluded from the analysis, as were patients who died within the first postoperative year. In South Korea, a final diagnosis of C71* is registered after the diagnosis has been confirmed through pathological examinations.

Quality of Life Before and After Craniotomy for Excision of Brain Tumors

QOL before and after craniotomy for the excision of brain tumors was evaluated using three criteria. If a study participant met any of the three criteria, they were considered to have experienced a deterioration in their QOL. First, job loss within one year after brain tumor surgery was evaluated. Although the NHIS database contains information regarding employment status before and after surgery, participants who were self-employed were not reflected in this study.

Second, participants' incomes before and in the first year after surgery were evaluated. In South Korean citizens should be registered in the NHIS[14] in one of two groups: an employee insured group and a self-employed insured group. The insurance premium for the employee insured group is determined in terms of income, whereas that for the self-employed insured group is determined in terms of property owned, income, and living standards. We derived the annual income level of all study participants at the time of hospital admission for surgery from data on the NHIS insurance premiums. The NHIS divides annual income levels into 20 groups according to 5% intervals (1st group: 0–5% [lowest] to 20th group: 95–100% [highest]). In addition, we divided the annual income level into four groups using quartile ratios (Q1, the lowest, to Q4, the highest).

Third, acquired new disability within the first postoperative year was evaluated. All individuals in South Korea with disabilities should be registered in the NHIS database in order to receive benefits from the social welfare system. Disabilities are classified into eight types: 1) physical, 2) brain lesion, 3) visual disturbance, 4) hearing, 5) speech, 6) intellectual, 7) mental, and 8) renal disorder disabilities. Additionally, the NHIS assigns each disability a grade from 1 to 6 according to severity, and two severity groups were considered in this study (1–3, severe disability and 4–6, mild to moderate disability). Patients with two different disabilities—for example, speech disorders with visual disturbance—can be registered as having two disabilities; the benefits they receive are calculated according to the sum of the

severity of each of the two disabilities. Physical disabilities are associated with limb disability, whereas brain lesion disabilities include people who are severely restricted in daily activities due to organic brain lesions such as traumatic brain injury, stroke, or cerebral palsy. The specific diseases that can be registered as brain disabilities are presented in eTable 1.

Study Endpoint

The primary endpoint was the prevalence of a deteriorating QOL (decreased income, job loss, and newly developed disability) among patients who underwent craniotomy for the excision of brain tumors. The secondary endpoint was 2-year all-cause mortality (additional 1-year mortality). The 2-year brain cancer mortality was defined as mortality where the primary cause was brain tumor (C71*).

Covariates

Demographic information, such as age and sex, was collected as covariates. Data regarding place of residence at time of surgery were extracted and classified as urban areas (Seoul and other metropolitan cities) and rural areas (all other areas). Data regarding location of the tumor in the brain were extracted using specific surgical ICD-10 codes, for example, cerebrum, except lobes and ventricles (C71.0); frontal lobe (C71.1); temporal lobe (C71.2); parietal lobe (C71.3); cerebral ventricle (C71.5); cerebellum (C71.6); brain stem (C71.7); overlapping site of brain (C71.8); and brain, unspecified (C71.9). As increased surgical case volume is known to decrease in-hospital morbidity and mortality,[15] the annual case volume of craniotomy for excision of brain tumor was collected in this study. The annual case volumes were divided into four groups using the quartile ratio (Q1: <14, Q2: 14–48, Q3: 49–140, and Q4: >140). The length of total hospital stays (LOS) and reoperation within 1-year were included as covariates. The reoperation category only included craniotomy for excision of the brain tumor. To reflect the comorbid status of patients, the Charlson comorbidity index was calculated using registered ICD-10 codes of individual underlying diseases, as shown in eTable 2. The Charlson comorbidity index was categorized into three groups (0–2, 3–4, and ≥ 5).

Statistical Analysis

The clinicopathological characteristics of the patients were presented as mean values with standard deviations for continuous variables and numbers with percentages for categorical variables. First, we constructed a multivariable logistic regression model for deteriorating QOL within 1-year after craniotomy for the excision of brain tumors. All covariates were included in the multivariate adjustment model. Next, we constructed multivariable Cox regression models for 2-year all-cause mortality after craniotomy for the excision of brain tumors. All covariates were included in multivariate adjustment models. The deterioration in QOL was divided into the three measures of loss of job, decreased income, and newly acquired disability, and a separate multivariable model was fitted to avoid multicollinearity with deterioration in QOL.

For disease-specific analyses, we performed multivariable Cox regression models for 2-year brain cancer mortality or other mortality. The results of the multivariable logistic regression model and multivariable

Cox regression model were presented as odds ratios (ORs) with 95% confidence intervals (CIs) and hazard ratios (HRs) with 95% CIs, respectively. The Hosmer–Lemeshow test was used to confirm that the goodness of fit of the multivariable logistic regression model was appropriate. Log–log plots were used to confirm that the central assumption of Cox proportional hazard models in the multivariable Cox regression models was satisfied. R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses, and *P*-values < 0.05, were considered statistically significant.

Results

Study Participants

There were 9,788 cases of craniotomy for the excision of brain tumors registered in the NHIS database from January 1, 2011, to December 31, 2017. After excluding 2,247 cases in which the patient underwent surgery ≥ 2 times and 684 pediatric patients younger than 18 years, 6,857 patients were initially screened. After excluding 2,005 patients who died within a year of surgery, 4,852 patients in total were finally included in the analysis. A flow diagram depicting patient selection is presented in Fig. 1. The clinicopathological characteristics of all the patients are presented in Table 1. A total of 1,433 patients (29.5%) died within 2 years of undergoing the craniotomy for brain tumor removal, 1,269 (26.2%) died from brain cancer, and 164 (3.45%) died from other primary causes.

Table 1
The clinicopathological characteristics of all the patients

Variable	Mean (SD) or number (%)
Age, year, mean (SD)	51.7 (15.0)
Sex, male, n (%)	2,595 (53.5)
Residence at surgery, n (%)	
Urban	2.186 (45.1)
Rural	2,665 (54.9)
Year of surgery, n (%)	
2011	606 (12.5)
2012	646 (13.3)
2013	684 (14.1)
2014	652 (13.4)
2015	658 (13.6)
2016	756 (15.6)
2017	849 (17.5)
Brain tumor location, n (%)	
Brain, unspecified	3,290 (67.8)
Cerebrum, except lobes and ventricles	387 (8.0)
Frontal lobe	421 (8.7)
Temporal lobe	178 (3.7)
Parietal lobe	96 (2.0)
Cerebral ventricle	29 (0.6)
Cerebellum	121 (2.5)
Brain stem	79 (1.6)
Overlapping site of brain	110 (2.3)
Annual case volume of craniotomy for brain tumor removal, n (%)	
Q1 < 14	1,372 (28.3)
Q2: 14–48	993 (20.5)

SD. Standard deviation, LOS, length of total hospital stays, CCI, Charlson comorbidity index

Variable	Mean (SD) or number (%)
Q3: 49–140	854 (17.6)
Q4 > 140	1,632 (33.6)
Reoperation within 1-year, n (%)	244 (5.0)
LOS, mean (SD)	19.9 (13.8)
CCI at craniotomy for brain tumor removal, n (%)	
0–2	623 (12.8)
3–4	2,046 (42.2)
≥ 5	2,182 (45.0)
Two-year mortality after craniotomy for brain tumor removal, n (%)	1,433 (29.5)
Mortality due to brain cancer	1,269 (26.2)
Other mortality	164 (3.4)
SD. Standard deviation, LOS, length of total hospital stays, CCI, Charlson comorbidity index	

Quality of Life After Craniotomy for Excision of Brain Tumors

Table 2 shows the changes to the QOL before and after the craniotomy for the excision of brain tumors: 2,273 patients (46.9%) who underwent the surgery experienced a deterioration in their QOL after surgery. Specifically, 595 (12.3%) lost their jobs within one year of the surgery, and 1,329 (27.4%) experienced decreased income. A total of 844 (17.4%) patients had newly acquired disabilities, and 764 (15.8%) had newly acquired brain disabilities. Table 3 shows the results of the multivariable logistic regression model for the QOL deterioration. Male sex (OR: 1.17, 95% CI: 1.04–1.31; $P = 0.009$), undergoing reoperation within one year (OR: 1.36, 95% CI: 1.02–1.79; $P = 0.033$), and a 1 day increase in LOS (OR: 1.02, 95% CI: 1.02–1.03; $P < 0.001$) were associated with a higher incidence of lower QOL.

Table 2
changes to the QOL before and after the craniotomy for the excision of brain tumors

Variable	Before surgery	After surgery
Presence of job[a], n (%)	1,415 (29.2)	820 (16.9)
Annual income level[b], n (%)		
Q1	801 (16.5)	704 (14.5)
Q2	922 (19.0)	807 (16.6)
Q3	1,145 (23.6)	1,168 (24.1)
Q4	1,664 (34.3)	1,687 (34.8)
Unknown	319 (6.6)	485 (10.0)
Total Disability[c], n (%)		
Mild to moderate	260 (5.4)	537 (11.1)
Severe	146 (3.0)	711 (14.7)
Type of disability, n (%)		
Physical disability	164 (3.4)	165 (3.4)
Brain disability	99 (2.0)	863 (17.8)
Visual disability	52 (1.1)	91 (1.9)
Hearing loss	38 (0.8)	44 (0.9)
Speech disability	4 (0.1)	18 (0.4)
Intellectual disorder	9 (0.2)	29 (0.6)
Mental disorder	9 (0.2)	9 (0.2)
Renal disability	7 (0.1)	9 (0.2)
2,273 (46.9%) experienced QOL worsening		
a: 595 (12.3%) loss their job after surgery		
b: 13,29 (27.4%) experienced decreased income		
c: 844 (17.4%) have new disability (764, 15.8% have new brain disability)		
QOL, quality of life		

Table 3
Multivariable logistic regression model for the QOL deterioration after craniotomy for excision of brain tumors

Variable	Multivariable model	*P*-value
	OR (95% CI)	
Age, year	1.00 (1.00, 1.00)	0.992
Sex, male	1.17 (1.04, 1.31)	0.009
Residence at surgery		
Urban	1	
Rural	1.09 (0.97, 1.22)	0.151
Year of surgery		
2011	1	
2012	1.17 (0.93, 1.48)	0.170
2013	1.14 (0.91, 1.43)	0.265
2014	1.11 (0.88, 1.39)	0.394
2015	1.27 (1.01, 1.60)	0.039
2016	1.20 (0.96, 1.50)	0.103
2017	1.33 (1.07, 1.65)	0.010
Brain tumor location		
Brain, unspecified	1	
Cerebrum, except lobes and ventricles	1.25 (1.01, 1.56)	0.045
Frontal lobe	0.92 (0.74, 1.14)	0.445
Temporal lobe	1.31 (0.96, 1.79)	0.087
Parietal lobe	1.16 (0.77, 1.76)	0.485
Cerebral ventricle	0.93 (0.44, 1.96)	0.855
Cerebellum	0.80 (0.55, 1.16)	0.238
Brain stem	0.97 (0.61, 1.52)	0.877
Overlapping site of brain	1.00 (0.67, 1.47)	0.982
Hosmer Lemeshow: chi-square. 11.55, df = 8, *P* = 0.172		

QOL, quality of life; OR, odds ratio; CI, confidence interval; LOS, length of total hospital stays, CCI, Charlson comorbidity index

Variable	Multivariable model	*P*-value
	OR (95% CI)	
Annual case volume of craniotomy for brain tumor removal		
Q1 < 14	1	
Q2: 14–48	1.10 (0.92, 1.31)	0.292
Q3: 49–140	1.14 (0.94, 1.37)	0.185
Q4 > 140	1.17 (0.99, 1.37)	0.056
Reoperation within 1-year	1.36 (1.02, 1.79)	0.033
LOS, day	1.02 (1.02, 1.03)	< 0.001
CCI at craniotomy for brain tumor removal		
0–2	1	
3–4	1.02 (0.85, 1.23)	0.815
≥ 5	1.09 (0.90, 1.32)	0.381
Hosmer Lemeshow: chi-square. 11.55, df = 8, *P* = 0.172		
QOL, quality of life; OR, odds ratio; CI, confidence interval; LOS, length of total hospital stays, CCI, Charlson comorbidity index		

Two-year Mortality

Table 4 shows the results of multivariable Cox regression for 2-year all-cause and cancer-specific mortality after craniotomy for excision of brain tumors. In the multivariable model, the deterioration in QOL was associated with a 1.41-fold increase in 2-year all-cause mortality (HR: 1.41, 95% CI: 1.27–1.57; *P* < 0.001). The other covariates in the multivariable models are listed in eTable 3. The survival plot derived from the multivariable model showed a similar trend (eFigure 1). Specifically, newly acquired disability was associated with a 1.80-fold increase in 2-year all-cause mortality (HR: 1.80, 95% CI: 1.59–2.03; *P* < 0.001), while loss of job (*P* = 0.353) and decreased income (*P* = 0.599) were not significantly associated.

Table 4
Multivariable Cox regression for 2-year all-cause and cancer-specific mortality after craniotomy for excision of brain tumors

Two-year mortality	Multivariable model	*P*-value
	HR (95% CI)	
All-cause mortality		
Any QOL worsening (model 1)	1.41 (1.27, 1.57)	< 0.001
Loss of job (model 2)	1.08 (0.92, 1.27)	0.353
Decreased income (model 2)	1.03 (0.92, 1.16)	0.599
Newly acquired disability (model 2)	1.80 (1.59, 2.03)	< 0.001
Brain cancer mortaity		
Any QOL worsening (model 3)	1.45 (1.29, 1.62)	< 0.001
Loss of job (model 4)	1.06 (0.89, 1.26)	0.548
Decreased income (model 4)	1.05 (0.92, 1.18)	0.490
Newly acquired disability (model 4)	1.89 (1.66, 2.14)	< 0.001
Other mortality		
Any QOL worsening (model 5)	1.14 (0.83, 1.57)	0.425
Loss of job (model 6)	1.29 (0.81, 2.07)	0.289
Decreased income (model 6)	0.92 (0.64, 1.33)	0.666
Newly acquired disability (model 6)	1.12 (0.74, 1.70)	0.600
Covariates included in the eTable 3: Year of surgery, reoperation within 1-year, sex, age, brain tumor location, LOS, CCI, residence at surgery, and annual case volume of surgery		
QOL, quality of life; HR, hazard ratio; CI, confidence interval; LOS, length of total hospital stays, CCI, Charlson comorbidity index		

For 2-year brain cancer mortality, increased associations were observed in patients with a deterioration in QOL (HR: 1.45, 95% CI: 1.29–1.62; $P < 0.001$) and newly acquired disability (HR: 1.89, 95% CI: 1.66–2.14; $P < 0.001$). However, the 2-year mortality due to other primary causes and deteriorating QOL had no significant association ($P = 0.425$).

Discussion

In this nationwide population-based cohort study, we showed that nearly half the patients who underwent a craniotomy for excision of brain tumors experienced a deterioration in their QOL in the first year after surgery: 595 (12.3%) lost their jobs, 1,329 (27.4%) earned less, and 844 (17.4%) developed new

disabilities. Male sex, reoperation, and longer LOS were significantly associated with a higher incidence of QOL deterioration. A deterioration in QOL was associated with a higher risk of 2-year mortality, especially for brain cancer mortality. Interestingly, of the QOL measures which we analyzed, job loss and decreased income were not associated with mortality, while newly acquired disability was.

In this study, brain disability had the highest proportion among the newly acquired disabilities (764/844, 90.5%) in the patient cohort. It has been reported that of the neurological sequelae observed among brain tumor survivors, cognitive dysfunction is the most serious.[16, 17] In a prospective cohort study of 188 patients, 16.0% of the patients had neurological complications after brain tumor surgery.[9] Another prospective cohort study reported that 11.4% of patients showed early postoperative neurosurgical complications after craniotomy for the excision of brain tumor.[18] However, the studies have focused on immediate neurological complications after brain tumor surgery.[9, 18] Yet other studies have reported that 5–6% of patients have long-term neurological sequelae after craniotomy for excision of brain tumor.[19, 20] In our study, 15.8% of patients had newly acquired disability after craniotomy for excision of brain tumors, which was higher than that reported in other studies.[19, 20] However, our study used a postoperative follow-up period of one year for all patients, resulting in more newly developed brain disabilities and postoperative sequelae being captured than in previous studies. Considering the importance of QOL among brain tumor survivors,[21] the longer duration of follow-up after surgery is a valuable aspect of this study.

Male sex, reoperation, and longer LOS were associated with a higher incidence of deteriorating QOL in this study. Although the exact mechanism of how sex impacts the development of neurological outcomes is not known, a previous study also reported that male sex had a higher risk of postoperative complications after brain tumor surgery.[22] A longer LOS means that the patient might have suffered from postoperative complications during hospitalization after the brain surgery. Similarly, another study reported that prolonged LOS was associated with a higher incidence of long-term complications in patients who underwent craniectomy for head injury.[23] Reoperation within one year of undergoing a craniotomy for brain tumor excision suggests that there might be an early tumor recurrence that requires surgery.[24] Therefore, patients who underwent reoperation were at a higher risk of their QOL deteriorating than other patients.

Curiously, neither decreased income nor loss of job was associated with 2-year all-cause or cancer mortality after craniotomy for the excision of brain tumors in this study. A previous study related that decreased income or loss of job was not associated with long-term mortality among survivors of extracorporeal membrane oxygenation in South Korea.[25] This lack of association might be due to the characteristics of the Korean public insurance system. The South Korean government pays almost all medical expenses for any individual who is diagnosed with severe and rare diseases such as cancer and severe intractable.[26] The government pays almost all treatment and examination charges for the disease category that malignant neoplasm of the brain (C71*) is included in; therefore, although a patient may be unemployed or have a lower income after the surgery, it would not affect their long-term mortality.

The results of our study showed that newly acquired disability was associated with higher long-term mortality. This is in keeping with a retrospective study that stated that long-term neurological problems, such as stroke and tumor recurrence, were associated with increased long-term mortality in patients with meningioma.[27] Another retrospective study reported that postoperative complications were associated with increased long-term mortality in children with brain tumor.[28] In addition to these findings, our analysis suggests that newly acquired disability, especially brain disability, among adult patients who underwent craniotomy for excision of brain tumor were in a higher risk population that needs special attention to prevent long-term mortality.

Our study has several limitations. First, we did not take into consideration the type of brain tumor, such as glioma and meningioma, since this information was not available from the NHIS database. Second, important variables, such as body mass index, operative time, and anesthetic technique, were not adjusted for in this study as this information, too, was not available from our database. Third, as the public insurance and social welfare systems in South Korea affected our results, our findings might not be generalizable to other countries. However, our findings suggest that with proper financial and social welfare support, newly acquired disability might be the only risk factor for increased mortality after brain tumor surgery. Finally, we did not consider the severity and stage of brain tumors, such those listed in the World Health Organization's classification system.[29]

In conclusion, at the 1-year follow-up, approximately half of the patients in this study experienced a lower QOL (unemployment, decreased income, and newly acquired disability) after craniotomy for excision of brain tumors. Among the three QOL factors we analyzed, newly acquired disability due to brain disability, was associated with increased 2-year all-cause and brain cancer mortality.

Declarations

Funding: None

Conflicts of interest/Competing interests: None

Availability of data and material: The data that support the findings of this study are available from National Health Insurance System, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the National Health Insurance System (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do). If someone wants to request the data from this study, please contact to corresponding author (ytjeon@snubh.org).

Code availability: Not applicable

Authors' contributions: TKO and YTJ contributed to the study design, analyzed the data, and drafted the first manuscript. IAS, SYL, HYC and JYK contributed to the data acquisition and critically revised the manuscript. All authors read and approved the final version of the manuscript.

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals: Not applicable

Ethics approval: The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (approval number: X-2104-679-901), and the National Health Insurance Service (NHIS) approved our study's data provision protocol (approval number: NHIS-2020-1-306).

Consent to participate: The need for informed consent was waived by the Institutional Review Board because the data were retrospectively analyzed using anonymized data from the NHIS database.

Consent for publication: Not applicable

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Figures

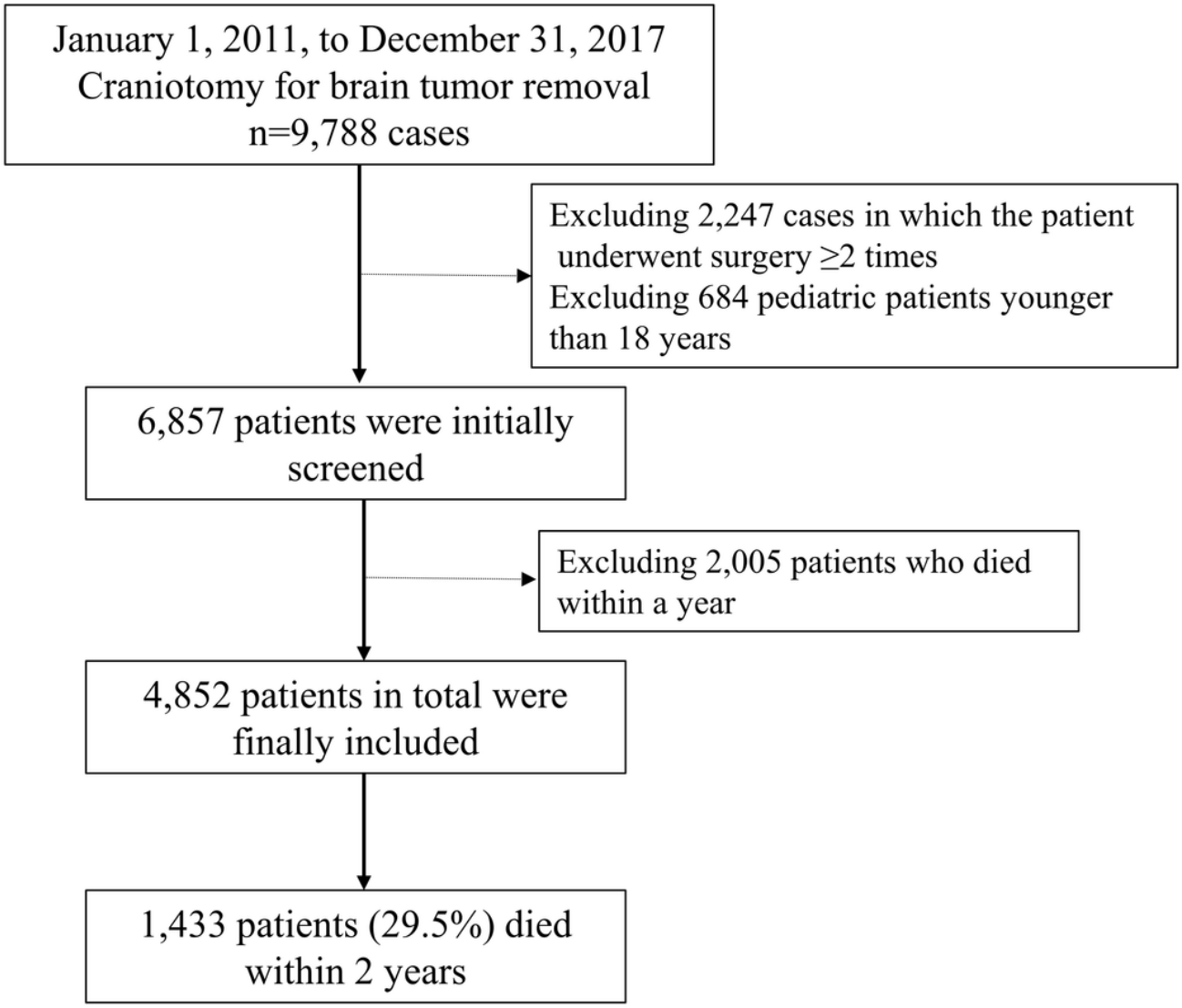

Figure 1

Flow diagram depicting the patient selection process

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