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Recurrent Thromboembolic Events after Ischemic Stroke in Patients with Primary Brain Tumors

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Abstract

Background—Stroke mechanisms and the risk of recurrent thromboembolism are incompletely understood in patients with primary brain tumors. We sought to better delineate these important clinical features.

Methods—We performed a retrospective cohort study of adults with primary brain tumors diagnosed with MRI-confirmed acute ischemic stroke at Memorial Sloan Kettering Cancer Center from 2005 to 2015. Study neurologists collected data on patients' cancer history, stroke risk factors, treatments, and outcomes. Stroke mechanisms were adjudicated by consensus. The primary outcome was recurrent thromboembolism (arterial or venous) and the secondary outcome was recurrent ischemic stroke. Kaplan-Meier statistics were used to calculate cumulative outcome rates, and Cox hazards analysis was used to evaluate the association between potential risk factors and outcomes.

Results—We identified 83 patients with primary brain tumors and symptomatic acute ischemic stroke. Median survival after index stroke was 2.2 years (interquartile range, 0.5–7.0). Tumors were mostly gliomas (72%) and meningiomas (13%). Most strokes were from unconventional mechanisms, particularly radiation vasculopathy (36%) and surgical manipulation (18%). Small-or large-vessel disease or cardioembolism caused 13% of strokes, while 29% were cryptogenic. Cumulative recurrent thromboembolism rates were 11% at 30 days, 17% at 180 days, and 27% at 365 days; while cumulative recurrent stroke rates were 5% at 30 days, 11% at 180 days, and 13% at 365 days. We found no significant predictors of outcomes.

Conclusions—Patients with primary brain tumors generally develop strokes from rare mechanisms and their risk of recurrent thromboembolism, including stroke, is high.

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Keywords

Stroke; thromboembolism; cancer and stroke; brain tumor; cerebrovascular disease

Introduction

Primary brain tumors are diagnosed in 77,000 people each year in the United States, and their incidence may be increasing.(1) Compared to other cancer types, primary brain tumors are associated with especially high morbidity and mortality.(2) However, advances in cancer treatments have led to longer survival in patients with malignant brain tumors.(3) Stroke, an important cardiovascular complication of cancer and a leading cause of adult disability, becomes more clinically relevant as these patients are living longer.(4)

Ischemic stroke portends a poor prognosis in patients with active systemic cancer. Roughly one-third of cancer patients with stroke develop a recurrent thromboembolic event by 3 months, and 13% develop recurrent ischemic stroke, which is approximately three times the expected rate in non-cancer patients.(5, 6) Moreover, the median survival after ischemic stroke in this population is 84 days.(5) The high risk of recurrent thromboembolism and death after stroke in the systemic cancer population is partly due to cancer-associated coagulopathy, a well-recognized non-traditional stroke mechanism correlating with heightened cancer activity.(7) It is uncertain whether patients with primary brain tumors and ischemic stroke also face an increased risk of recurrent thromboembolism, as prior small studies have suggested that stroke in this population is more often from non-coagulopathic mechanisms such as radiation vasculopathy and surgery.(8–10) However, childhood cancer survivors with prior cranial radiation face an elevated stroke risk.(11–13) Additionally, some primary brain tumors have been associated with hypercoagulability.(14, 15)

We analyzed a large, contemporary cohort of patients with primary brain tumors and acute ischemic stroke to better characterize stroke mechanisms in this population. In addition, we sought to evaluate the risk and predictors of recurrent thromboembolism, stroke, and death among these patients. Our prespecified hypothesis was that rates of recurrent stroke and other thromboembolism in patients with primary brain tumors and acute ischemic stroke would be elevated when compared to the general stroke population, similar to systemic cancer patients.

Materials and Methods

Study Design

This was a retrospective cohort study of adult patients with primary brain tumors diagnosed with acute ischemic stroke at Memorial Sloan Kettering Cancer Center (MSKCC). Patients were included if their stroke was diagnosed in the inpatient or outpatient setting at an MSKCC facility, including Memorial Hospital, a 470-bed academic, quaternary-care cancer hospital in Manhattan, and several satellite ambulatory care clinics throughout New York, New Jersey, and Connecticut. Patients treated at MSKCC are actively followed for clinical outcomes, particularly thrombotic events and death, regardless of where the outcome occurs.

Therefore, medical records from outside institutions are systematically collected and archived electronically to facilitate comprehensive care. Consequently, patients hospitalized for stroke at non-MSKCC hospitals who then saw MSKCC providers as an outpatient were also included as long as adequate clinical information and brain imaging were available for review. The MSKCC Institutional Review Board approved this study and granted a waiver of informed consent because of minimal risk to patients.

Study Subjects

Patients aged 18 years or older with a primary brain tumor and subsequent diagnosis of acute ischemic stroke at MSKCC between January 1, 2005 and December 31, 2014 were included. These patients were identified by searching the Department of Neurology's comprehensive clinical database for any patient diagnosed with "primary brain tumor," "primary central nervous system tumor," "stroke," "ischemic stroke," or "transient ischemic attack," and by reviewing MSKCC's administrative claims database for patients with *International Classification of Diseases-9-Clinical Modification* diagnosis codes for primary brain tumors (191.x, 192.0, 192.1, 192.8, 192.9, 225.0, 225.1, 225.2, 225.8, 225.9) and acute ischemic stroke (433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436). These codes were selected based on use in prior studies on similar topics.(5, 16) "Transient ischemic attack" was included in the query of the departmental clinical database; however, only patients with MRI-confirmed acute arterial ischemic stroke were included in the study cohort.

Query results were reviewed manually. Patients met eligibility criteria if they had an MRI-confirmed arterial ischemic stroke, a preceding diagnosis of primary brain tumor, and adequate clinical information regarding stroke presentation and diagnostic evaluation. Ischemic stroke was defined as a new neurologic deficit with corresponding evidence of acute infarction on brain MRI in the absence of clinical or radiologic indication of a non-cerebrovascular etiology. Because patients with primary brain tumors undergo routine surveillance imaging, which may lead to incidental findings including stroke, we also collected information on patients with MRI evidence of acute infarction in the absence of new neurologic deficits. These patients were classified as having silent brain infarctions and were analyzed in a separate secondary analysis.

Patients with stroke diagnosed by CT alone were excluded given the lack of imaging specificity. Primary brain tumor was defined as any primary tumor, whether intra-axial or extra-axial, malignant or benign, occurring within the cranium. We excluded patients with active malignancies outside of the central nervous system metastatic to the brain, as we were interested specifically in the primary brain tumor patient population.

Measurements

Data were collected regarding patients' demographics, vascular risk factors, oncologic history, antithrombotic medication use, stroke evaluation and treatment, hospital discharge disposition, modified Rankin Scale (mRS) at discharge, and post-discharge follow-up. Brain tumors were categorized as glioma versus non-glioma. Gliomas were classified as high-grade and low-grade by WHO criteria.(17) Investigators certified in mRS ascertainment(18)

utilized all available information from clinical and physical therapy notes to determine the discharge mRS. Abiding by guidelines for the proper conduct of retrospective research,(19) variables were defined in a data dictionary by investigator consensus and several mock abstraction sessions were performed before official chart reviews. In addition, data were collected on standardized data abstraction forms, which were also designed iteratively by investigator consensus.

Patients' strokes were categorized by the modified TOAST (Trial of Org 10172 in Acute Stroke Treatment) study criteria.(20) Stroke mechanisms, including those unique to the cancer population, were predefined in the study data dictionary. Perioperative stroke was defined as stroke occurring within 30 days of a major or minor operation. For these patients, when the stroke was found immediately following surgery and was in or contiguous with the surgical field, and no alternative cause was identified or suspected, the mechanism of stroke was classified as surgical manipulation. In keeping with prior studies,(8) stroke from radiation vasculopathy was defined as stroke ipsilateral to the patient's site of prior brain radiation, with no other identified mechanism of stroke. Imaging evidence of intracranial stenosis was not required for the diagnosis of radiation vasculopathy because radiation can cause small vessel vasculopathy,(21, 22) and lacunar-appearing strokes have been reported in patients after radiation.(23) Each patient's stroke mechanism was independently adjudicated by two neurologists (NSP and JEB) with a board-certified stroke neurologist (BBN) serving as the final arbitrator.

Outcomes

All available inpatient and outpatient medical records, including transmitted outside institution records and telephone encounters, were reviewed from the time of the index stroke through December 31, 2015. Our primary outcome was any recurrent thromboembolic event, defined as in our prior studies as a composite of any recurrent ischemic stroke, transient ischemic attack, myocardial infarction, deep venous thrombosis, pulmonary embolism, or systemic arterial thrombosis or embolism.(5) Secondary outcomes were recurrent ischemic stroke, intracranial hemorrhage, symptomatic intracranial hemorrhage, major bleeding, and death.

Statistical Analysis

Patient characteristics were evaluated with standard descriptive statistics. Cumulative outcome rates were determined by Kaplan-Meier methods, and patients were censored at the time of last follow-up, death, or end of study on December 31, 2015. Multivariable Cox proportional hazard modeling was used to evaluate the association between several prespecified covariates and clinical outcomes. The following covariates were chosen based on data from prior studies and biological plausibility: age at time of index stroke, sex, nature of tumor (glioma versus non-glioma), prior stroke or TIA, and radiation-associated vasculopathy as the underlying index stroke mechanism.(13, 24, 25) The number of variables was determined based on the anticipated sample size. Variables were entered and kept in the multivariable model regardless of significance at the univariate level. The threshold of statistical significance was $p < 0.05$.

Several prespecified secondary analyses were performed. We evaluated the effect of recurrent thromboembolism on survival while adjusting for age, sex, and high-grade glioma tumor type. We examined outcome rates only among patients with gliomas and, separately, those patients who had received vascular endothelial growth factor inhibitors within 30 days prior to their index stroke. Lastly, recurrent thromboembolism rates were measured among the secondary cohort of patients with silent brain infarctions, and these rates were compared using the log-rank test to the primary cohort of patients with symptomatic strokes. All statistical analyses were performed using Stata MP Version 12 (StataCorp, College Station, TX).

Results

Patient Characteristics

Of 269 patients identified for review, 83 patients with primary brain tumors and symptomatic acute ischemic stroke met our eligibility criteria and were included in the final analysis (Figure 1). These 83 patients constituted 0.8% of the 10,468 unique patients seen at MSKCC for primary brain tumor during the study period. Their median age was 60 years (interquartile range, 51–67) and 53% were women (Table 1). Vascular risk factors were common, particularly hypertension (53%) and hyperlipidemia (40%). Most patients had gliomas (n=60, 72%), particularly high-grade gliomas (n=49, 59%), or meningiomas (n=11, 13%). Other primary brain tumor types included medulloblastoma (n=2), ependymoma (n=2), pituitary adenoma (n=2), and primary central nervous system lymphoma (n=1). Most patients (71%) had received head or neck radiation therapy, and 31% had received non-surgical cancer treatment within 30 days of their stroke, including 12 with vascular endothelial growth factor inhibitor therapy and 20 with other chemotherapy. There were 16 patients (19%) who had their index stroke within 30 days of surgery. The median number of days between surgery and stroke diagnosis was 1 day (IQR, 0.25–1.75).

The median time from primary brain tumor diagnosis to the index stroke was 2.0 years (interquartile range [IQR], 0.7–8.0). At the time of the index stroke, 13 patients (16%) were taking an antithrombotic medication. Diagnostic stroke evaluations included intracranial or extracranial vessel imaging in 69%, an echocardiogram in 69%, and inpatient cardiac rhythm evaluation in 81%. After excluding patients who died during hospitalization and those with strokes due to surgical manipulation, 77% had vessel imaging, 77% had an echocardiogram, and 77% had inpatient cardiac rhythm evaluation.

Demographics, stroke characteristics, and tumor characteristics were similar between patients who developed a recurrent thromboembolism after index stroke and those who did not except that cancer treatment in the 30 days before index stroke was less common in patients ultimately diagnosed with recurrent thromboembolism (10% vs. 39%, p=0.01) (Table 1).

Index Stroke Mechanisms and Treatments

Conventional stroke mechanisms were rarely identified, with 48 patients (58%) diagnosed with a known but unconventional etiology and 24 (29%) diagnosed with cryptogenic stroke

(Table 2). By TOAST criteria, 9 patients (11%) had small-vessel disease, 1 patient (1%) had cardiac embolism, and 1 patient (1%) had large-artery atherosclerosis. The most common unconventional stroke mechanisms were radiation vasculopathy (36%) and surgical manipulation (18%). The median time from radiation therapy completion to the index stroke was 2.1 years (IQR, 1.0–8.1). The discharge mRS could be determined in 72 patients (87%), and the median was 3 (IQR, 3–4). An antithrombotic medication was prescribed at discharge to 74% of patients, and 56% were prescribed a statin; prescription rates were higher when excluding patients with stroke due to surgical manipulation—81% were prescribed an antithrombotic medication and 62% a statin. Of those discharged on an antithrombotic medication, 52 (88%) received an antiplatelet medication and 7 (12%) an anticoagulant medication.

Primary Analysis

The median study follow-up time was 1.1 years (IQR, 0.4–3.1), and the median number of documented patient follow-up encounters during this period was 10 (IQR, 5–20). Over this period, 48 (58%) patients died. Median survival from the index stroke was 2.2 years (IQR, 0.5–7.0). For patients who were alive at last follow-up, the median study follow-up time was 2.7 years (IQR, 1.1–4.3). After the index stroke, 12 patients were diagnosed with subsequent ischemic stroke, 2 with TIA, and 8 with venous thromboembolism. Cumulative rates of any recurrent thromboembolism were 11% at 30 days, 14% at 90 days, 17% at 180 days, and 27% at 365 days (Figure 2). Cumulative rates of recurrent ischemic stroke were 5% at 30 days, 8% at 90 days, 11% at 180 days, and 13% at 365 days. Major bleeding was diagnosed in 6 patients (7%), all with intracranial hemorrhage; of these, 3 patients were on aspirin. Recurrent thromboembolism or stroke (ischemic or hemorrhagic) was the cause of death for 5 (10%) of the 48 patients who died during follow-up. Specifically, 2 patients died from a recurrent ischemic stroke, 2 died from an intracranial hemorrhage, and one died from pulmonary embolism.

In our prespecified univariable and multivariable Cox analyses, we found no significant predictors of recurrent thromboembolism (Table 3) or recurrent stroke (Table 4). A nonsignificant trend towards increased recurrent stroke risk was observed in patients with radiation vasculopathy as the mechanism of their index stroke (hazard ratio 2.4, 95% confidence interval 0.7–7.8).

Secondary Analyses

In exploratory multivariable analysis, recurrent thromboembolism was non-significantly associated with reduced survival after adjusting for age, sex, and high-grade glioma tumor type (hazard ratio, 1.59; 95% confidence interval, 0.80–3.14). Cumulative rates of recurrent thromboembolism (log-rank test: p=0.95) and recurrent ischemic stroke (log-rank test: p=0.56) were similar for patients with gliomas and those with other brain tumors. Of 12 patients who had received vascular endothelial growth factor inhibitor therapy within 30 days prior to the index stroke, none had recurrent thromboembolism.

We identified an additional 23 patients with silent brain infarction in addition to the 83 in the primary analysis. This group did not differ significantly in patient demographics, clinical

characteristics, or stroke mechanisms. After silent brain infarction, cumulative recurrent thromboembolism rates were 9% at 90 days, 19% at 180 days, and 19% at 365 days; these cumulative incidence rates were not significantly different compared to patients with symptomatic strokes (log-rank test: p=0.91). Similarly, cumulative rates of recurrent ischemic stroke were 4% at 90 days, 15% at 180 days, and 15% at 365 days, which again were not significantly different compared to patients with symptomatic strokes (log-rank test: p=0.48). Median survival was nonsignificantly longer in patients with silent brain infarction compared to those with symptomatic strokes (3.9 years versus 2.2 years; log-rank test: $p = 0.54$).

Discussion

In a contemporary cohort of patients with primary brain tumors and acute ischemic stroke, we found high rates of recurrent thromboembolism and stroke, similar to what has been reported in patients with systemic cancer.(5, 26, 27) Patients with primary brain tumors experienced a short-term recurrent stroke rate that was approximately double the recurrent stroke rate observed in the general population.(6) We did not find any significant independent predictors of recurrent thromboembolism. Patients with radiation vasculopathy appeared to face double the risk of recurrent stroke, although this trend was nonsignificant. Additionally, we found a nonsignificant trend towards reduced survival in patients who developed recurrent thromboembolism. These associations did not reach statistical significance likely due to the relatively small number of patient outcomes.

In our study, stroke mechanisms in patients with primary brain tumors were often unique to the specific treatments they received, particularly cranial radiotherapy and neurosurgical manipulation, which together accounted for 54% of strokes. These results are consistent with prior smaller studies that have also reported radiation vasculopathy and surgical injury to be common causes of stroke in the primary brain tumor population.(8, 10) However, the perioperative stroke rate in our cohort was less than in previous studies, perhaps because we included all primary brain tumor types (not just gliomas) and we excluded incidental strokes from our primary analysis.(8–10) We also found that patients with radiation vasculopathy had a non-significant trend towards a higher recurrent stroke rate. Prior research has shown that cervicocephalic radiation is a strong risk factor for cerebrovascular complications in children and adults.(8, 11–13) In our population, that risk was realized at a median of only two years after completion of radiotherapy, emphasizing that most patients with brain tumors will survive into the period of risk. Interestingly, stroke mechanisms in this cohort of patients with primary brain tumors differed markedly when compared to previous studies of patients with systemic cancer, in whom cryptogenic strokes are common.(5) In the systemic cancer population, many of these cryptogenic strokes are thought to arise from non-bacterial endocarditis,(28, 29) a form of cancer-related hypercoagulability.(30, 31) The paucity of cryptogenic and radiographically cardioembolic-appearing strokes in our cohort suggests that this mechanism is uncommon in patients with primary brain tumors.

We are unaware of any previously published studies reporting thromboembolism and stroke recurrence rates in patients with primary brain tumors. In a prior study of patients with systemic cancer, the cumulative 6-month recurrent thromboembolism rate was 37%, and the

cumulative 6-month recurrent stroke rate was 16%.(5) This is in contrast to the general stroke population, which has a 1-year cumulative recurrent stroke rate of approximately 4.8%.(6) The unconventional mechanisms of stroke in systematic cancer and primary brain tumor patients likely contribute to the high risk of recurrent events. Alternatively, it is possible that patients with cancer are not treated as aggressively for their stroke as patients without cancer; however, this is unlikely to fully explain the disparity in stroke rates between groups, as patients in this and prior studies generally had thorough diagnostic evaluations and regularly received secondary stroke prevention.(5, 32)

In secondary analyses, we found similarly high rates of recurrent thromboembolism and stroke in patients with silent brain infarctions as compared to those with symptomatic strokes. Emerging data in non-cancer patients suggest that silent brain infarctions are associated with a two-fold increased risk of subsequent stroke.(33) Therefore, identification of a silent brain infarction in a primary brain tumor patient might serve as an opportunity to prevent a disabling stroke through initiation of targeted stroke prevention therapies.(34)

This study has several limitations. First, this was a retrospective study, so some outcomes of interest may have been missed. In addition, MSKCC is not a certified stroke center; therefore, some patients with acute stroke may have been taken elsewhere and the data not captured. These limitations would result in an underestimation of recurrence risks. Second, the study was performed at an urban, quaternary care, cancer center such that the results may not generalize to other settings. Third, although our cohort was relatively large for this topic, our multivariable regression analyses may have been underpowered as evidenced by the wide confidence intervals. Finally, we did not collect long-term functional outcome data, so we are unable to determine the impact of recurrent thromboembolism and ischemic stroke on patient-centered outcomes such as disability and quality of life.

Conclusions

Stroke mechanisms in patients with primary brain tumors are unique when compared to both patients with systemic cancer and the general population. These patients survive for years after their index stroke but face an increased risk for recurrent thromboembolism and ischemic stroke. Improving secondary stroke prevention in patients with primary brain tumors may reduce disability.

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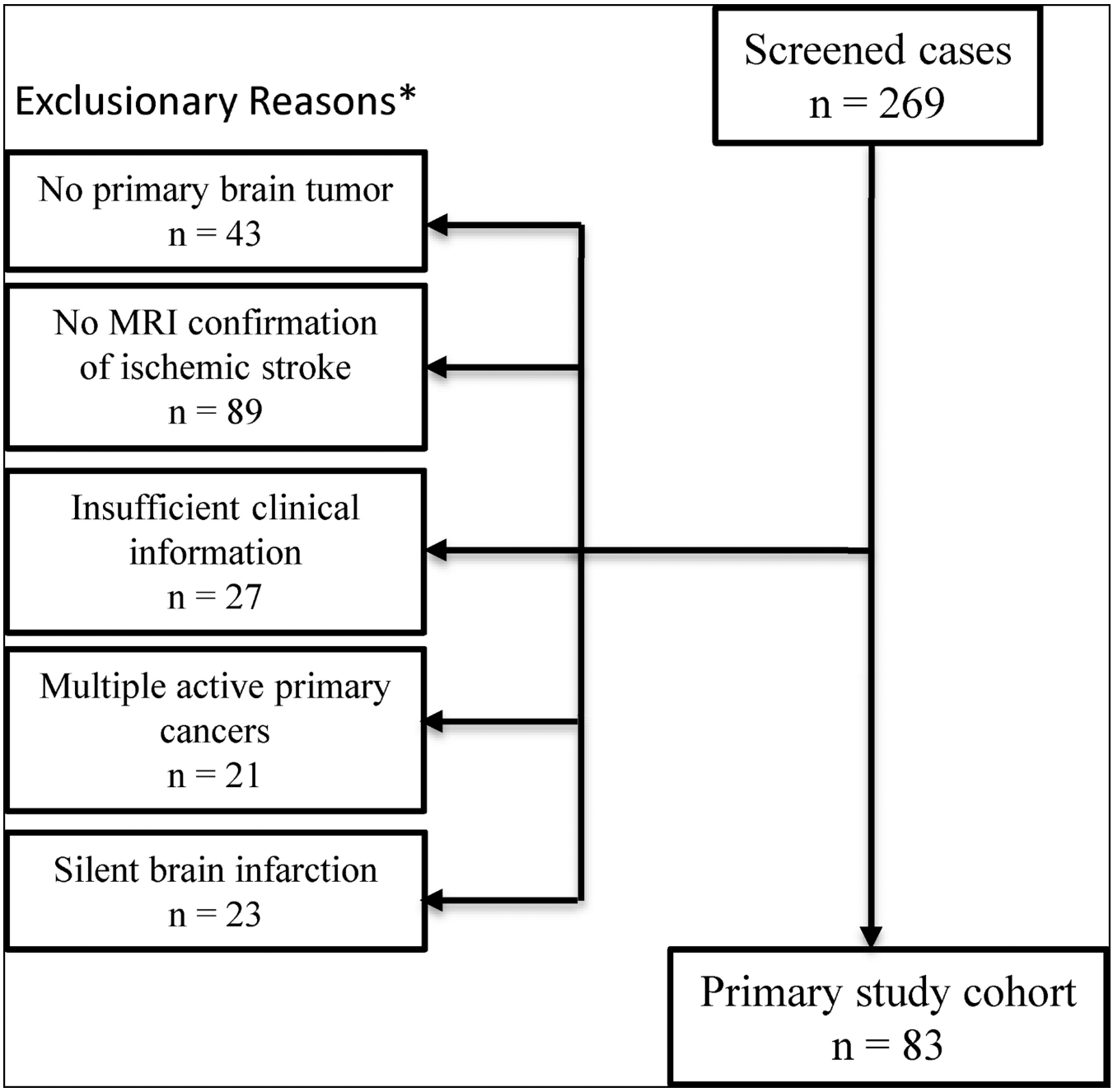

Figure 1. Study Cohort Eligibility Flowsheet

Flow chart diagram describing patient selection for study. *Some patients had multiple reasons for exclusion.

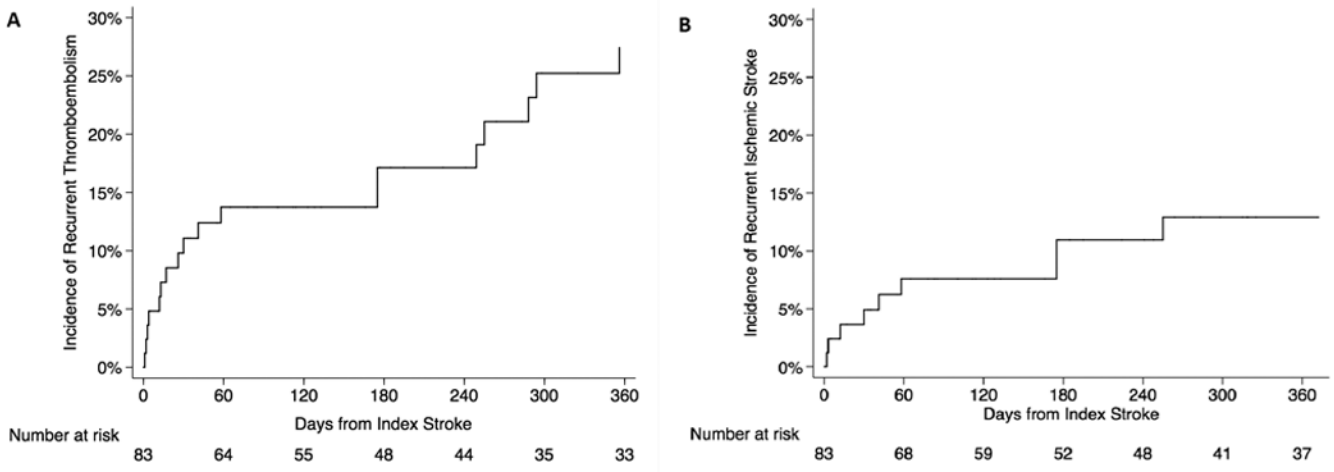

Figure 2. Cumulative Rates of Recurrent Thromboembolism and Ischemic Stroke in Patients with Primary Brain Tumors and Acute Ischemic Stroke

Cumulative rates of recurrent thromboembolism (Panel A) and recurrent ischemic stroke (Panel B) in patients with primary brain tumors after acute ischemic stroke.

Table 1

Characteristics of Patients with Primary Brain Tumors and Ischemic Stroke, Stratified by Recurrent Thromboembolism

Characteristic[a]	Total (n = 83)	Recurrent Thromboembolism (n=21)	No recurrent Thromboembolism (n=62)	*P*-value
Age, years, median (IQR)	60 (51–67)	59 (45–64)	61 (53–68)	0.34
Women	44 (53%)	9 (43%)	35 (56%)	0.20
Race-ethnicity				1.00
White	72 (87%)	18 (86%)	54 (87%)	
Black	4 (5%)	1 (5%)	3 (5%)	
Other	7 (8%)	2 (10%)	5 (8%)	
Comorbidities				
Hypertension	44 (53%)	10 (48%)	34 (55%)	0.35
Hyperlipidemia	33 (40%)	5 (24%)	28 (45%)	0.07
Diabetes	9 (11%)	1 (5%)	8 (13%)	0.28
Coronary disease	6 (7%)	2 (10%)	4 (6%)	0.48
Atrial fibrillation	1 (1%)	0 (0%)	1 (2%)	0.75
Prior stroke or TIA	7 (8%)	1 (5%)	6 (10%)	0.43
History of smoking	26 (31%)	6 (29%)	20 (32%)	0.49
Oncological history				
Glioma	60 (72%)	14 (67%)	46 (74%)	0.34
High-grade glioma	49 (59%)	11 (52%)	38 (61%)	0.32
Low-grade glioma	11 (13%)	3 (14%)	8 (13%)	0.57
Meningioma	11 (13%)	3 (14%)	8 (13%)	0.57
Other	12 (14%)	4 (19%)	8 (13%)	0.36
Recent cancer treatment[b]	26 (31%)	2 (10%)	24 (39%)	0.01
Prior head or neck RT	59 (71%)	17 (81%)	42 (68%)	0.19
Antiplatelet at discharge	52 (63%)	12 (57%)	40 (65%)	0.36
Anticoagulant at discharge	7 (8%)	1 (5%)	6 (10%)	0.43

Abbreviations: IQR, interquartile range; TIA, transient ischemic attack; RT, radiotherapy.

[a] Data are presented as number (%) unless otherwise specified.

[b] Non-surgical treatment within the last 30 days.

Table 2

Specific Stroke Mechanisms in Patients with Primary Brain Tumors and Acute Ischemic Stroke

Specific stroke mechanism	No. (%)
Radiation vasculopathy	30 (36%)
Cryptogenic	24 (29%)
Surgical manipulation	15 (18%)
Small-vessel disease	9 (11%)
Extrinsic compression of vessel by tumor	3 (4%)
Intracranial large-artery atherosclerosis	1 (1%)
Atrial fibrillation	1 (1%)

Table 3

Univariable and Multivariable Cox Proportional Hazards Models of Factors Associated with Recurrent Thromboembolism

Variable	Univariable HR	95% CI	Multivariable HR	95% CI
Age	1.23	0.51–2.97	1.21	0.48–3.03
Female gender	0.69	0.29–1.64	0.64	0.26–1.56
Prior stroke or TIA	0.52	0.70–3.89	0.50	0.06–3.86
Radiation vasculopathy[a]	1.27	0.54–2.99	1.34	0.55–3.26
Glioma tumor type	0.97	0.39–2.43	0.97	0.37–2.54

Abbreviations: HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack.

[a]Radiation vasculopathy refers to a patient's index stroke mechanism.

Table 4

Univariable and Multivariable Cox Proportional Hazards Models of Factors Associated with Recurrent Ischemic Stroke

Variable	Univariable HR	95% CI	Multivariable HR	95% CI
Age	1.04	0.31–3.41	1.06	0.31–3.65
Female gender	0.45	0.13–1.50	0.41	0.11–1.44
Prior stroke or TIA	0.97	0.12–7.54	1.00	0.12–8.50
Radiation vasculopathy[a]	1.98	0.62–6.28	2.41	0.74–7.80
Glioma tumor type	0.71	0.22–2.27	0.73	0.21–2.54

Abbreviations: HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack.

[a]Radiation vasculopathy refers to a patient's index stroke mechanism.