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

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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 magnetic resonance imaging-confirmed acute ischemic stroke at the 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, .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, whereas 29% were cryptogenic. Cumulative recurrent thromboembolism rates were 11% at 30 days, 17% at 180 days, and 27% at 365 days, whereas 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. *Conclusion:* Patients with primary brain tumors generally develop strokes from rare mechanisms, and their risk of recurrent thromboembolism, including stroke, is high. **Key Words:** 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 with 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

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event by 3 months, and 13% develop recurrent ischemic stroke, which is approximately 3 times the expected rate in noncancer 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 nontraditional 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 noncoagulopathic 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 with 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 magnetic resonance imaging (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 radiological indication of a noncerebrovascular 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, oncological history, antithrombotic medication use, stroke evaluation and treatment, hospital discharge disposition, modified Rankin Scale (mRS) at discharge, and postdischarge follow-up. Brain tumors were categorized as glioma versus nonglioma. Gliomas were classified as high-grade and low-grade by the World Health Organization criteria.[17] Investigators certified in mRS ascertainment[18] used 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