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CME

Stroke in patients with cancer

Incidence and etiology

D.M. Cestari, MD; D.M. Weine, MD; K.S. Panageas, DrPh; A.Z. Segal, MD; and L.M. DeAngelis, MD

Abstract—*Objective:* To assess the incidence and type of strokes in patients with cancer at Memorial Sloan–Kettering Cancer Center. *Methods:* Retrospective review of all ischemic strokes diagnosed by a neurologist and confirmed by neuroimaging between February 1997 and April 2001 was conducted. Age, gender, cancer diagnosis and stage, and vascular risk factors were recorded. NIH Stroke Scale and modified Rankin Scale scores were calculated retrospectively. Stroke etiology was assigned independently by two neurologists using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. *Results:* Ninety-six patients with a confirmed stroke were identified. The median age was 67, and 61.5% were men. The distribution of vascular risk factors was comparable with that seen in large stroke trials. Lung cancer (30%) was the most common primary tumor followed by brain and prostate cancer (9% each). Strokes were embolic in 52 (54%) and nonembolic in 44 (46%). Eleven of 12 tested patients had an elevated D-dimer level, but in only 3 patients could a definitive diagnosis of nonbacterial thrombotic endocarditis be made. The median survival was 4.5 months (95% CI 2.8 to 9.5) from the diagnosis of stroke; 25% of patients died within 30 days. Treatment had no effect on survival. *Conclusions:* Embolic strokes are the commonest cause of stroke in patients with cancer, due partially to hypercoagulability, whereas atherosclerosis accounted for only 22% of stroke in this population. Outcome was primarily determined by the underlying malignancy and the patient's neurologic condition.

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Cerebrovascular complications including hemorrhage and infarction are second only to metastases in frequency of CNS lesions in large autopsy series of patients with cancer.[1] Several studies have examined the various causes of cerebrovascular disease in patients with cancer,[1-4] but no study has evaluated stroke etiology with modern neuroimaging or assessed the prognosis of these patients after stroke. There is no agreement on whether cancer-specific causes such as hypercoagulability are more important than traditional risk factors such as hypertension in causing cerebrovascular disease in the patient with cancer.[1,2] Understanding these factors is important for stroke prevention and treatment in this population. A retrospective study of stroke in patients with cancer assessed several factors including extent of neoplastic disease, cancer type, stroke subtype or stroke etiology, and the effects of etiology and treatment on outcome of these patients.

Methods. We reviewed the clinical, pathologic, and radiologic records of patients with cancer diagnosed with nonhemorrhagic stroke by a neurologist at Memorial Sloan–Kettering Cancer Center (MSKCC) between January 1997 and April 2001. Patients were identified from the database of the Department of Neurology to ensure that all patients had a thorough neurologic evaluation and all potential confounding neurologic diagnoses were excluded in each patient. Our database captures all patient encounters with a neurologist at MSKCC and catalogues a maximum of three neurologic diagnoses. We compared our data with the inpatient population seen at MSKCC during the same time interval. We also compared the incidence of cerebrovascular disease at MSKCC with that obtained from two large urban tertiary referral centers, the New York Presbyterian Hospital at both the Cornell and the Columbia campuses. General information on stroke incidence was obtained from the medical records departments of all three institutions.

For the MSKCC patients, age, gender, cancer diagnosis and stage, and vascular risk factors were collected. Neurology resident and attending consultation notes were used to calculate retrospectively NIH Stroke Scale (NIHSS) and modified Rankin Scale scores.[5,6] Neuroimaging reports of relevant CT or MRI were reviewed. Patients were excluded from the study if a stroke was not confirmed by CT or MRI or if the patient had a cerebral hemorrhage or TIA. The charts of included patients were reviewed, and all data relevant to stroke evaluation in that patient were identified and recorded. This included EKGs, ultrasound/MR angiography (MRA) of head/neck, Holter monitoring, echocardiogram, and laboratory data (basic chemistries, complete blood count, coagulation studies, blood culture, and disseminated intravascular coagulopathy panel, which includes prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer; D-dimer is elevated when values exceed 0.21 μg/mL). The clinical course and date of death or last follow-up were recorded; death due to stroke was defined as occurring within 30 days of stroke presentation.

Stroke risk factors including hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, and tobacco use were recorded. Stroke etiology was assigned independently by two neurologists using criteria modified from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) Study and finalized by consensus.[7] The diagnosis was assigned using all imaging and laboratory data obtained as part of the stroke evaluation. An infarct was characterized as embolic if it radiographically involved the cortex with a typical wedge-shaped appearance or if multiple lesions were identified in the distribution of more than one vascular territory. Embolic infarcts were subdivided into cardioembolic if an EKG demonstrated atrial fibrillation or if an echocardiogram demonstrated thrombus. The diagnosis of endocarditis required documentation of valvular lesions on echocardiogram and was further classified as infectious (IE) if positive blood cultures were obtained

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and nonbacterial thrombotic endocarditis (NBTE) if blood cultures were negative and there was no other source of emboli. Echocardiograms were obtained in 61 patients, and all were transthoracic; transesophageal echocardiograms (TEEs) were not performed in any patient, frequently because of coagulopathy or acute illness. Single new subcortical infarcts were characterized as a large-vessel stroke if there was ultrasound or MRA evidence of large-vessel involvement. A diagnosis of small-vessel disease was made when a new typical lacunar infarct, appropriate to the patient's symptoms, was identified on CT or MR scan. Subcortical strokes were classified as cardioembolic if a clear cardiac source was identified. Strokes were classified as "other" for such causes as perioperative stroke and designated "unknown" in the case of incomplete evaluation.[7-9] All categories were evaluated and then grouped into either embolic (cardioembolic, other embolic, IE, NBTE) or nonembolic (large-vessel, small-vessel, other, unknown) events.

Medications the patient was taking at onset of stroke and treatment initiated after stroke were recorded for each patient. Treatment was categorized as either antiplatelet (aspirin, aspirin/dipyridamole, clopidogrel), anticoagulation (heparin, low molecular weight heparin, warfarin), both (any combination of the two groups), or none.

Associations between two categorical variables were assessed using the χ^2 test. Survival time was defined from the date of stroke to the date of death or last follow-up. Overall survival distributions were estimated using the Kaplan-Meier method and compared using the log-rank test.

Results. *Patient characteristics.* Stroke was diagnosed in 195 patients between January 1997 and April 2001. Ninety-nine patients were excluded from further analysis because the clinical impression of a stroke could not be confirmed on imaging or the stroke was in the past and not the reason for the consultation. Ninety-six patients were identified with a confirmed acute stroke during the study period. This represented 0.12% of all admissions to MSKCC. In contrast, stroke was the diagnosis in 1.58 and 1.91% of all patients admitted by the Cornell and Columbia campuses, respectively, of the New York Presbyterian Hospital.

Table 1 *Comparison of MSKCC patient characteristics with those from major stroke trials*

Characteristics	MSKCC patients, n = 96	Stroke trials[23,32–35]
Age, y		
Median	67	63–69
Range	27–91	
NIH Stroke Scale		
Median	5	
Range	0–47	
Rankin		
Median	2.0	
Range	0–5	
Sex, %		
Men	61	57–63
Women	39	37–43
Vascular risk factor, %		
Hypertension	53	44–68
Tobacco	32	14–52
Coronary artery disease	25	18–30
Diabetes mellitus	19	11–33
Hypercholesterolemia	18	—
Alcohol abuse	7	3–4
Atrial fibrillation	5	16–35
None	15	—

MSKCC = Memorial Sloan–Kettering Cancer Center.

Table 2 *Cancer frequency in MSKCC patients with stroke from January 1997 through April 2001*

Primary malignancy	No. (%) of patients with stroke
Lung	29 (30)*†‡
Intracranial	9 (9)
Prostate	9 (9)*
Breast	4 (4)
Lymphoma	6 (6)
Leukemia	6 (6)
Gynecologic	6 (6)†
Bladder	6 (6)‡
Gastroesophageal	6 (6)
Other	19 (20)

Lymphoma includes both Hodgkin disease and non-Hodgkin lymphoma. Percentage is determined according to the number of patients with each primary.

* Includes five patients with prostate plus lung.
† Includes one with gynecologic and lung cancer.
‡ Includes two with bladder plus lung cancer.
MSKCC = Memorial Sloan–Kettering Cancer Center.

The majority of MSKCC patients were men (61.5%), and the median age was 67 (table 1). The median NIHSS score at diagnosis was 5 (0 to 47), and the median Rankin score was 2.0 (0 to 5). The frequency of vascular risk factors was similar in MSKCC patients and in patients enrolled in large clinical stroke trials. The most common was hypertension in 50 (53%) patients, 30 (32%) had a history of tobacco use, and 18 (19%) had diabetes mellitus. Fifty-four (57%) patients had two or more risk factors, and 14 (15%) had no risk factors for stroke other than cancer. A subset analysis was done on patients with lung cancer because they represented the largest single group. Lung cancer was associated with tobacco use ($p < 0.01$) and diabetes mellitus ($p = 0.05$) possibly related to glucocorticoid use for management of chronic obstructive pulmonary disease, but there was no increased incidence of coronary artery disease.

Primary cancer. Patients with stroke had 31 different cancers; eight patients had two cancers (table 2). Lung (30%), brain (9%), and prostate (9%) were the most common cancers. In comparison, only 11% of inpatients seen at MSKCC during this same period had lung cancer, 2% had intracranial tumors, and 10% had prostate cancer. Breast cancer accounted for 18% of admissions but only 4% of those with stroke.

Of the cancer patients with stroke, 88 of 94 (94%) had active systemic tumor and 44 (47%) had metastatic disease; 2 patients had missing extent-of-disease information. Six (6%) had brain or leptomeningeal metastases at stroke diagnosis. Of these six patients, four had known CNS metastases prior to their stroke evaluation, and two were

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Table 3 *Stroke etiology*

Stroke etiology	No. (%) of patients
Embolic	52 (54)
Cardioembolic	14 (15)
D-Dimer positive	1
IE	2 (2)
NBTE	3 (3)
D-Dimer positive	2
Other embolic	33 (34)
D-Dimer positive/negative	6/1
Nonembolic	44 (46)
Large vessel	10 (10)
Small vessel	11 (12)
Other	5 (5)
D-Dimer positive	2
Unknown	18 (19)

IE = infectious endocarditis; NBTE = nonbacterial thrombotic endocarditis.

found to have clinically silent brain metastases during their stroke evaluation.

Signs, symptoms, and etiologies. Presenting symptoms and signs included hemiparesis in 70 (74%), aphasia/dysarthria in 48 (51%), and visual field deficit in 25 (26%); ataxia was present in 10 (11%), headache in 8 (8%), and seizure in 8 (8%).

Based on the TOAST criteria, 52 (54%) strokes were embolic and 44 (46%) were nonembolic (table 3). The etiology was cardioembolic in 14 (15%), IE in 2 (2%), NBTE in 3 (3%), other embolic in 33 (34%), large vessel in 10 (10%), small vessel in 11 (12%), other in 5 (5%), and unknown in 18 (19%).

MRA was performed in 23 patients, carotid ultrasound in 30, and both in 4 patients. MRA was normal in 12 and carotid ultrasound in 23 patients. Large-vessel disease such as severe carotid stenosis or occlusion was confirmed on MRA or ultrasound in all 10 patients diagnosed with large-vessel disease. In six patients, distal arterial occlusions were identified on MRA, confirming an embolic etiology.

Coagulopathy played a role in 11 patients, 6 of whom had lung cancer and 5 nonlung cancers. Eleven of 12 patients tested (92%) had elevated D-dimer (values 2.0 to 16.0 μg/mL) identified in their blood. All patients but one had D-dimer drawn as part of their stroke evaluation; one patient had a D-dimer level of 8 μg/mL 2 days prior to the stroke. Two of these patients had a definitive diagnosis of NBTE, six had other embolic strokes, one had a cardioembolic cause, and two were in the "other" category.

Survival and outcome. Neurologic outcome could be ascertained for 95 patients; 1 had missing information. At discharge, most patients had neurologic improvement (58%) from their stroke; however, only 2% had returned to their baseline function. Fifteen percent had a fixed deficit that did not improve, and 25% died within 30 days of their stroke.

The median overall survival was 4.5 months (95% CI 2.8 to 9.5) for all 96 patients from the diagnosis of stroke.

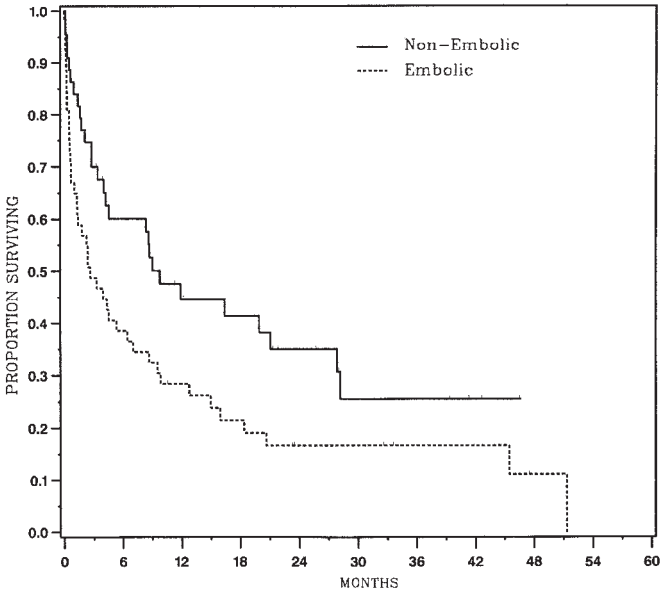

*Figure 1. Overall survival stratified by type of stroke: embolic vs nonembolic stroke (*p = *0.03).*

Rankin score, stroke etiology, primary cancer diagnosis, and the presence of metastatic disease affected survival. Patients with an embolic stroke had a median survival of 2.6 months, whereas those with nonembolic etiologies had a median survival of 9.8 months ($p = 0.03$) (figure 1). There was no difference in outcome between patients with cardiogenic or other sources of embolism. However, patients with embolic strokes had a significantly higher incidence (66%; $p = 0.03$) of metastatic disease. Patients with a modified Rankin score of ≤2 had a median survival of 11.9 months, and those with a score of ≥3 had a median survival of 0.6 month (18 days) ($p < 0.001$) (figure 2). Survival was also inversely associated with increasing NIHSS score ($p < 0.001$). Patients with lung cancer had a worse survival (median of 3.3 months) than patients with

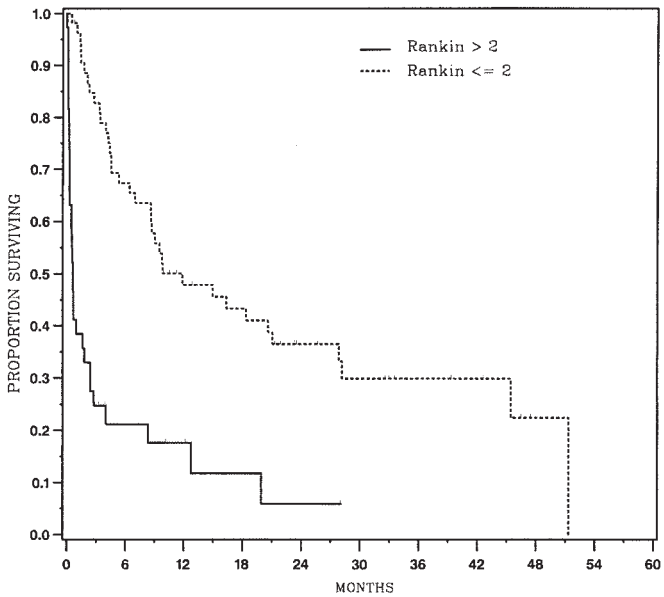

*Figure 2. Overall survival stratified by Rankin score (*p < *0.001).*

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other primaries (median of 9.0 months) ($p < 0.01$). Metastatic disease decreased survival ($p < 0.01$); those without metastatic disease had a median survival of 15.0 months, and those with metastases survived a median of only 2.8 months. Thirty-day mortality was not affected by stroke type (embolic vs nonembolic; $p = 0.06$), cancer type (lung vs other; $p = 0.16$), or metastases ($p = 0.34$) but was affected by modified Rankin score (≤ 2 vs ≥ 3; $p < 0.001$).

Treatment. Treatment for stroke of any kind was administered in 59 patients (62%). The decision to initiate treatment was not based on primary cancer (lung vs nonlung; $p = 0.65$) but was significantly related to stroke etiology and Rankin score. Embolic strokes were treated with an antiplatelet agent, anticoagulant, or both more frequently (71 vs 51%; $p = 0.05$) than nonembolic events. Patients with modified Rankin scores of ≤ 2 had treatment more frequently than patients with modified Rankin scores of ≥ 3 ($p < 0.001$). There was no significant relationship between type of treatment initiated and stroke, but the number of patients in each category is small. Overall survival was not improved with the institution of any form of stroke-specific treatment, but the data are not sufficiently powered to draw a meaningful conclusion.

Discussion. This report represents the largest clinical series of stroke in patients with cancer. In an autopsy study of 3,426 patients dying with systemic cancer, 30% had CNS lesions; cerebral infarction was found in 256 of these patients, but only 117 of them had a symptomatic stroke.[1] Symptomatic nonhemorrhagic stroke is a well-recognized complication in patients with cancer; however, our data suggest stroke accounts for less than one-tenth of the number of admissions to a major cancer institution compared with a large general academic medical center. Even accounting for selection bias, stroke was uncommon in our cancer population. We had stringent criteria for stroke diagnosis in this study and included only those patients evaluated by the neurology service who had a confirmed infarct on neuroimaging. Patients with possible stroke who were not seen by the neurology service, patients who were not imaged, and those with negative imaging (e.g., the scan was obtained too soon after the onset of symptoms and not repeated) were not captured in this study. We included only those patients with sufficient evaluation that a stroke type and possible etiology could be assigned, that other processes such as metastases could be excluded, and in whom an outcome could be determined. If we estimate that half of stroke patients were excluded from this study, stroke would account for only 0.2 to 0.3% of all admissions to MSKCC.

Autopsy studies demonstrated the most common cause of cerebral infarction in patients with cancer was atherosclerosis, but the majority of these infarctions (76.7%) were asymptomatic.[1] In contrast, the most common single cause of symptomatic cerebral infarction in this population was NBTE, which accounted for 27% of strokes followed by intravascular coagulation (24%) and atherosclerosis (14.5%).[1] Therefore, pathologically proven hypercoagulable states were responsible for 51% of symptomatic strokes. In a clinical study of stroke in 33 patients with cancer, large-vessel atherosclerosis was the most frequent cause of symptomatic strokes and NBTE was not diagnosed in a single patient.[2] Our patients had a vascular risk factor profile that was typical of most large series of stroke patients, except for the low incidence of atrial fibrillation, but our patients had more embolic events and less evidence of intrinsic vascular disease than most stroke series report. In our series, atherosclerosis played a definitive role in only 22% of patients. Large-vessel disease was identified in 10% and small-vessel disease in only 12% of patients, a substantially lower frequency than seen in large series of stroke in the general population and in the prior clinical study of patients with cancer.[2,21-23] Our patients were not studied prospectively, and they did not undergo a comprehensive uniform vascular or hemostatic evaluation to assign stroke etiology. Therefore, it is possible that embolic strokes were overestimated and intrinsic vascular disease underrepresented because it was not detected.[10,11] However, >60% of patients in this series who had a carotid ultrasound or MRA had a normal study, and our 22% frequency of symptomatic stroke due to atherosclerosis in patients with cancer is very comparable with the 14.5% incidence found at autopsy.[1]

D-Dimer is a direct measure of activated coagulation and fibrinolysis and is used in many studies as a measure of hypercoagulability. In several large series of patients with cancer, an elevated D-dimer can be identified in 30.5 to 90% depending on whether metastatic disease was present or not.[12-14] Therefore, in these patients, it can be difficult to attribute a stroke definitively to hypercoagulability based on D-dimer alone. NBTE can elevate the D-dimer and cause stroke due to hypercoagulability, but in this study, the incidence of NBTE was low. Based on autopsy data, NBTE is underestimated in the clinical setting owing to the difficulty of establishing the diagnosis with certainty. The best means of diagnosing NBTE is with TEE demonstrating valvular vegetations in a setting with negative blood cultures.[3,15-19] None of our patients had a TEE as part of the stroke evaluation, so the low incidence of stroke definitively attributed to NBTE is not surprising. An elevated D-dimer level is seen in a wide variety of conditions with intravascular clotting, including stroke itself, particularly embolic stroke with levels of ≥ 2.0 μg/mL.[20] Our 11 patients with an elevated D-dimer all had values of ≥ 2.0 μg/mL; 9 were given a diagnosis of embolic stroke, and 2 were in the "other" category. Therefore, the increased D-dimer in our patients may have been due to the stroke itself, but in one patient, the D-dimer was increased 2 days prior to his stroke and in two others, NBTE was diagnosed, suggesting cancer-induced hypercoagulability, at least in these three patients. Therefore, an elevated D-dimer level alone may not be used to assign stroke etiology. More patients with cancer and stroke need to be

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studied to understand the utility of this test in the cancer population, and additional studies in a large number of cancer patients with stroke may help to clarify this issue.

Once stroke occurred in a patient with cancer, regardless of etiology, the overall prognosis was poor. The median survival was only 4.5 months, and survival was strongly correlated with initial neurologic disability, similar to the general population with stroke.[24] In our analysis, we also found that patients with strokes of embolic origin had a particularly bad outcome. In most stroke series, cardioembolic strokes are associated with a worse prognosis, but in this study, only 27% of all embolic events were cardiogenic in origin, and other embolic events carried an equivalently bad prognosis. Metastatic disease may have contributed to the short survival of patients with embolic stroke, and in many patients, the stroke seemed to herald the terminal event. Advanced malignancy is often associated with a hypercoagulable state, which in turn may lead to embolic events; elevated D-dimers in these patients are also associated with elevated serum angiogenic factors, which may play an undefined role in cerebrovascular disease in patients with cancer.[13] Widespread and uncontrollable cancer was often a reason not to treat a stroke or pursue a vigorous evaluation in some of our patients. Palliative care was often instituted; these patients accounted for many of the 25% who died within 30 days of stroke onset.

Patients with lung cancer had a high frequency of stroke, particularly embolic events. This may be partially attributed to the higher prevalence of diabetes and smoking in the lung cancer population, although 48% of these patients had no history of tobacco use. Many of these embolic events were likely due to hypercoagulability, particularly because 55% of those with documented disseminated intravascular coagulation had lung cancer. In addition, tumor emboli, which can be diagnosed only pathologically, can also arise from a pulmonary neoplasm, leading to stroke.[3]

Patients with intracranial tumors were the second most common group to develop stroke. They accounted for nearly 10% of stroke patients in our study, despite representing only 2% of all patients seen at MSKCC during this period. Cranial irradiation can cause accelerated atherosclerosis of neck and intracranial vessels.[25,26] This is usually thought to take many years, even decades, to develop. However, the strokes seen in our patients occurred within a few years of diagnosis and treatment in all patients. Accelerated atherosclerosis has been reported in irradiated children and may occur more rapidly in adults as well.[27] Brain tumor patients have a high incidence of venous thromboembolic disease, as evidenced by a 20 to 25% incidence of deep vein thrombosis and pulmonary embolus.[28,29] However, they are not known to have an increased risk of stroke. We do not have sufficient data to determine whether these patients had a patent foramen ovale that may enable venous clot to cause a cerebral infarct. Brain injury can activate the coagulation cascade, causing a state of hypercoagulability with the release of thromboplastin-like factors from the CNS.[30] Hemostatic changes can also occur following surgery for a brain tumor, and these changes may contribute to stroke in this population.[31]

Regardless of stroke etiology, treatment appeared to have little impact on outcome, probably because stroke treatment has no effect on the underlying cancer, which was metastatic in almost half of patients. However, secondary prevention might benefit a subset of patients, not only prolonging survival but also preserving neurologic function. Only a prospective study could address that question.

The results of this study demonstrate that a variety of factors influence the outcome of a patient with cerebrovascular disease in the setting of an underlying neoplasm. Severity of malignancy, type of cancer, stroke etiology, and disability following stroke all influence prognosis. Stroke is seen with reasonable frequency among patients with cancer, particularly those with lung or other solid tumors, and clinical stroke etiology in these patients was frequently embolism rather than small-vessel disease. Although only a small number of our patients had confirmed cancer-related hypercoagulability, it likely played a critical role in many of our patients, given the prevalence of NBTE and associated findings of hypercoagulability in the cerebral vessels of patients with cancer at autopsy.[1] However, the nature of the hypercoagulable state and the mechanisms by which it leads to stroke require a prospective study.

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