Intracerebral and subarachnoid hemorrhage in patients with cancer

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ABSTRACT

Objective: To analyze the risk factors, presentation, etiologies, and outcomes of adult cancer patients with intracranial hemorrhage (IH).

Methods: We analyzed 208 patients retrospectively with the diagnosis of IH from the Memorial Sloan-Kettering neurology database from January 2000 through December 2007. Charts were examined for clinical and radiographic data. Survival was calculated using the Kaplan-Meier method. Survival between groups was compared via the log-rank test. Logistic regression models were used to assess for prognostic indicators of 30- and 90-day mortality.

Results: There were 181 intracerebral and 46 subarachnoid hemorrhages. Sixty-eight percent of patients had solid tumors, 16% had primary brain tumors, and 16% had hematopoietic tumors. Hemiparesis and headache were the most common symptoms. Intratumoral hemorrhage (61%) and coagulopathy (46%) accounted for the majority of hemorrhages, whereas hypertension (5%) was rare. Median survival was 3 months (95% confidence interval [CI] 2–4), and 30-day mortality was 31%. However, nearly one-half of patients were completely or partially independent at the time of discharge. Patients with primary brain tumors had the longest median survival (5.9 months, 95% CI 2.9–11.8, $p = 0.05$). Independent predictors of 30-day mortality were not having a primary brain tumor, impaired consciousness, multiple foci of hemorrhage, hydrocephalus, no ventriculostomy, and treatment of increased intracranial pressure.

Conclusions: Intracranial hemorrhage in patients with cancer is often due to unique mechanisms. Prognosis is poor, but comparable to intracranial hemorrhage in the general population. Aggressive care is recommended despite high mortality, because many patients have good functional outcomes. *Neurology*® 2010;74:494–501

GLOSSARY

CI = confidence interval; DIC = disseminated intravascular coagulation; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IH = intracranial hemorrhage; INR = international normalized ratio; ITH = intratumoral hemorrhage; IVH = intraventricular hemorrhage; MSKCC = Memorial Sloan-Kettering Cancer Center; PTT = partial thromboplastin time; SAH = subarachnoid hemorrhage.

Cerebrovascular disease is the second most common CNS complication in patients with cancer.¹ Intracranial hemorrhage (IH) accounts for nearly one-half of cerebrovascular events and is more likely to be symptomatic than ischemic lesions.¹ The causes of IH in the cancer population differ from the general population and vary based on the type of malignancy. Solid tumors typically cause IH from intratumoral hemorrhage (ITH), representing an average of 3.1% of spontaneous IH in large autopsy series, whereas hematologic malignancies may cause IH from coagulopathy or leukostasis.^{1–3} IH generally occurs late in the course of malignancy, although it may be the first manifestation of cancer.^{4–10} Most hemorrhages are intraparenchymal and can vary in presentation.^{1,11–13}

IH in patients with cancer is often viewed as a catastrophic and terminal event, although limited data on outcome exist.^{14,15} Most existing literature is autopsy based or precedes the modern era of neuroimaging. Moreover, advances in oncologic therapies and neurointensive

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care have significantly changed the demographics, pathophysiology, and prognosis of these patients. The objective of this retrospective study was to analyze the clinical manifestations, causes, and treatments of IH in adult patients with cancer.

METHODS We reviewed the records of all cancer patients with a radiologically confirmed diagnosis of intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH) who were evaluated by a neurologist between January 2000 and December 2007; patients were identified from the Department of Neurology database. Subdural and epidural hemorrhages were included only if they coexisted with an ICH or SAH.

We excluded patients who had postoperative hemorrhages. Patients with incomplete records and those aged 17 years or younger were also excluded. Patients with recurrent hemorrhages were included only once at the time of first hemorrhage. Most patients had excellent follow-up, and only 6 were not seen by a Memorial Sloan-Kettering Cancer Center (MSKCC) provider after October 2007. We had functional and vital status for all patients; disposition after ITH was known for all but 4. The number of patients with missing data for each clinical and laboratory variable is shown in table 1.

Clinical features, vascular risk factors, type and stage of cancer, prior and current cancer treatment, presentation, radiographic information, therapy, prognostic factors, and outcome were collected. Cancer diagnoses were confirmed pathologically in all but 2 patients, 1 with a meningioma and 1 with a brainstem glioma. The presence of active disease and systemic or CNS metastases were documented. Prior cranial irradiation or craniotomy and current chemotherapeutic agents were noted. Laboratory values at diagnosis were recorded, including complete blood count, glucose, creatinine, international normalized ratio (INR), partial thromboplastin time (PTT), D-dimer, and fibrinogen. The presence of antiplatelet or anticoagulant agents was documented. All patients had CT, MRI, or both. Hemorrhage location was categorized as supratentorial, infratentorial, lobar, basal ganglia, brainstem, or cerebellum. Hemorrhage size could not be determined because of the diffuse and multifocal nature of many bleeds. Presence and type of herniations and hydrocephalus were also noted. Etiology of hemorrhage was determined by the reviewer and could include multiple diagnoses. ITH consisted of any hemorrhage into an underlying tumor. Coagulopathy was diagnosed if any of the following parameters were fulfilled: platelets $<100/\text{mm}^3$, INR >1.5 , PTT >45 seconds, disseminated intravascular coagulation (DIC) (fibrinogen <200 mg/dL and D-dimer >290 ng/dL), or full-dose low-molecular-weight heparin within the past 48 hours. Leukostasis was defined as a white blood cell count greater than $100 \times 10^3/\text{mm}^3$.

Treatment of hemorrhage was recorded. Treatment for increased intracranial pressure (ICP) consisted of osmotic diuresis or hyperventilation. The functional status of patients at discharge was determined retrospectively and categorized as completely independent, partially independent, completely dependent, death, and unknown. The disposition and survival of patients were also documented.

Survival was analyzed using the Kaplan-Meier method. Survival time was defined from the date of hemorrhage to the date of death or last follow-up. Survival between groups was compared using the log-rank test. Logistic regression models analyzed 30- and 90-day mortality, and predictors of mortality

Table 1 Demographics of cancer patients with intracerebral and subarachnoid hemorrhage at MSKCC from January 2000 through December 2007^a

Characteristic	No. (%) of patients, N = 208
Age, y	
Median	61
Range	19–91
Gender	
Male	116 (56)
Female	92 (44)
Race	
White	161 (77)
Black	19 (9)
Hispanic	15 (7)
Other	9 (4)
Unknown	4 (2)
Location of hemorrhage	
Intracerebral	181 (87)
Subarachnoid	46 (22)
Intraventricular	28 (14)
Subdural	18 (9)
Epidural	0 (0)
Multiple compartments	46 (22)
Active cancer	193 (93)
Metastases	147 (71)
Brain tumor (primary or metastatic)	91 (44)
Vascular risk factors	
Tobacco	94 (45)
Hypertension	90 (43)
Cranial irradiation	54 (26)
Diabetes mellitus	23 (11)
Alcohol abuse	14 (7)
Coronary or kidney disease	11 (5)
Bleeding diatheses	
Anticoagulant use	40 (19)
Unknown	1
Antiplatelet use	27 (13)
Thrombocytopenia (platelets <100) ^b	59 (28)
50–99	19
20–49	15
<20	25
INR >1.5	28 (14)
Unknown	2
PTT >40	26 (13)
Unknown	3
DIC	4 (2)

Abbreviations: DIC = disseminated intravascular coagulation; INR = international normalized ratio; MSKCC = Memorial Sloan-Kettering Cancer Center; PTT = partial thromboplastin time.

^aPercentages are rounded to the nearest decimal point and thus may not add up to 100.

^b $\times 10^3/\text{mm}^3$.

Table 2 Cancer type in patients with intracranial and intratumoral hemorrhage at MSKCC^a

Primary malignancy	Patients with IH, n = 208	Patients with ITH, n = 127
Solid tumors	141 (68)	98 (77)
Melanoma	32 (15)	31 (24)
Lung	29 (14)	26 (20)
Breast	14 (7)	9 (7)
Prostate	11 (5)	2 (2)
Renal	8 (4)	8 (6)
Colorectal	6 (3)	2 (2)
Other	41 (20)	20 (16)
Liquid tumors	33 (16)	2 (2)
Leukemia	13 (6)	1 (1)
Lymphoma	9 (4)	1 (1)
Myelodysplastic syndrome	5 (2)	0
Other	6 (3)	0
Primary brain tumors	34 (16)	27 (21)
Glioma	24 (12)	23 (18)
Glioblastoma multiforme	14 (7)	14 (11)
Oligodendroglioma	6 (3)	6 (5)
Astrocytoma	4 (2)	3 (2)
Primary CNS lymphoma	4 (2)	2 (2)
Meningioma	4 (2)	0
Other	3 (1)	2 (2)

Abbreviations: IH = intracranial hemorrhage; ITH = intratumoral hemorrhage; MSKCC = Memorial Sloan-Kettering Cancer Center.

^aData are expressed as no. (%). Percentages are rounded to the nearest decimal point and thus may not add up to 100.

univariately. Factors univariately significant at the $\alpha \leq 0.05$ level were included in a stepwise logistic regression model with entry and exit levels set at 0.10 to produce the final multivariate analyses. All analyses were performed in SAS 9.2 (SAS Institute Inc., Cary, NC).

Standard protocol approvals, registrations, and patient consents. This study was approved by the MSKCC Institutional Review Board.

RESULTS Patient characteristics. ICH or SAH was diagnosed in 357 patients with cancer at MSKCC between January 2000 and December 2007, but only 208 met our inclusion criteria. There were 116 (56%) men and 92 (44%) women (table 1). The median age was 61 (range 19–91) years, and 77% of patients were Caucasian. One hundred eighty-one patients (87%) had ICH, 46 (22%) had SAH, and 28 (14%) had intraventricular hemorrhage (IVH). Eighteen (9%) had coexistent subdural hemorrhage, and none had epidural hemorrhage. Forty-six patients (22%) had hemorrhage into multiple brain compartments; the most frequent compartmental

combinations were ICH plus SAH plus IVH (n = 13) and ICH plus SAH (n = 11). Cerebrovascular risk factors included tobacco use (45%), hypertension (43%), diabetes mellitus (11%), and ethanol abuse (7%). Forty patients (19%) were on therapeutic anticoagulation, but only 6 (3%) were supratherapeutic; 27 (13%) patients were on antiplatelet agents at the time of hemorrhage.

Cancer type. Patients with IH had 42 different cancers; 20 patients had 2 or more cancers. The cancer contributing to hemorrhage was a solid tumor in 141 patients (68%), a primary brain tumor in 34 (16%), and a hematologic tumor in 33 (16%) (table 2). Melanoma (15%), lung (14%), glioma (12%), breast (7%), and leukemia (6%) were the most common primary malignancies. Of the 24 gliomas, there were 14 glioblastomas, 6 oligodendrogliomas, and 4 other astrocytomas. Renal cell (4%), testicular (2%), hepatocellular (1%), and thyroid (1%) cancers were infrequent despite their known propensity to bleed. Most patients had both active disease (93%) and systemic metastases (71%) at the time of hemorrhage. Patients with primary brain tumors were the youngest cohort, with 47% aged 50 years or younger, whereas only 23% of patients with a solid tumor and 7% of those with hematopoietic tumors were in this age range. The median time from cancer diagnosis to hemorrhage was 28 months for solid tumors, 22 months for hematologic tumors, and 6 months for primary brain tumors. Almost half the patients (n = 91, 44%) had a known primary or metastatic brain tumor at the time of hemorrhage. Fifty-four patients (26%) had received prior cranial radiation therapy, and 37 (18%) had received prior craniotomy. Half the patients (n = 104) had received chemotherapy within the past 4 weeks. Five received antiangiogenic therapy with bevacizumab (n = 4) or sunitinib (n = 1); the patient receiving sunitinib had ITH with coagulopathy, but none of the patients receiving bevacizumab had ITH.

Presentation. The majority of patients were symptomatic (94%) from the hemorrhage (table 3). Patients with primary brain tumors (18%) were more likely to be asymptomatic than patients with solid (4%) or hematopoietic tumors (3%). Hemiparesis (48%), headache (41%), and impaired consciousness (34%) were the most common symptoms or signs; few patients had seizures (17%) or coma (6%). Only 5% of patients were acutely hypertensive with a systolic blood pressure greater than 180 mm Hg or a diastolic blood pressure greater than 120 mm Hg at time of ICH. The mean white blood cell count was 7.8×10^3 cells/mm³, and the mean creatinine was 1.1 mg/dL. Only 7% of patients had a serum glucose greater than 200 mg/dL. Nineteen patients had mild

Table 3 Presentation and etiology of intracranial hemorrhage in patients with cancer at MSKCC^a

Characteristic	All patients, n = 208	Solid tumor, n = 141	Hematologic tumor, n = 33	Brain tumor, n = 34
Symptomatic	196 (94)	136 (97)	32 (97)	28 (82)
Hemiparesis	100 (48)	68 (48)	15 (46)	17 (50)
Headache	86 (41)	64 (45)	11 (33)	11 (32)
Decreased consciousness	70 (34)	42 (30)	20 (61)	8 (24)
Encephalopathy	38 (18)	25 (18)	5 (15)	8 (24)
Nausea or vomiting	37 (18)	31 (22)	2 (6)	4 (12)
Seizure	36 (17)	26 (18)	5 (15)	5 (15)
Aphasia	34 (16)	20 (14)	7 (21)	7 (21)
Hemisensory disturbance	29 (13)	23 (16)	5 (15)	1 (3)
Visual field disturbance	23 (11)	15 (11)	4 (12)	4 (12)
Coma	12 (6)	6 (4)	5 (15)	1 (3)
Etiology				
ITH	127 (61)	98 (70)	2 (6)	27 (79)
Coagulopathy	95 (46)	55 (39)	26 (79)	14 (41)
ITH and coagulopathy	44 (21)	33 (23)	1 (3)	10 (29)
Trauma	12 (6)	6 (4)	5 (15)	1 (3)
Hypertension	11 (5)	9 (6)	1 (3)	1 (3)
Hemorrhagic conversion	8 (4)	4 (3)	4 (12)	0 (0)
Venous thrombosis	5 (2)	1 (1)	1 (3)	3 (9)
Aneurysmal rupture	4 (2)	3 (2)	1 (3)	0 (0)
Multifactorial	69 (33)	45 (32)	11 (33)	13 (38)

Abbreviations: ITH = intratumoral hemorrhage; MSKCC = Memorial Sloan-Kettering Cancer Center.

^aData are expressed as no. (%).

thrombocytopenia ($50\text{--}99 \times 10^3$ platelets/mm³), 15 had moderate thrombocytopenia ($20\text{--}49 \times 10^3$ /mm³), and 25 had severe thrombocytopenia ($<20 \times 10^3$ /mm³) (table 1). Twenty-eight patients (14%) had INR values greater than 1.5, and 26 (13%) had PTT values greater than 40 seconds. DIC was documented in 4 patients, 2 of whom had acute promyelocytic leukemia.

Radiographic diagnosis was established in all patients by CT (24%), MRI (12%), or both (64%). Most patients bled into the intracerebral compartment (87%), and nearly half (n = 91, 44%) had multiple foci of hemorrhage. IH was usually supratentorial and equally dispersed between hemispheres of the brain (left 52%, right 48%). Infratentorial hemorrhages occurred in 37 patients (18%) and were most common in the cerebellum (n = 29). Herniation was seen radiographically in 50 patients (24%), 38 subfalcine, 19 uncal, 14 transtentorial, and 6 tonsillar. Hydrocephalus of any form was seen in 37 patients (18%).

Etiology. ITH (61%) and coagulopathy (46%) were the most common causes of IH in our population (table 3). Less common causes were head trauma

(6%), hypertension (5%), hemorrhagic conversion of an ischemic stroke (4%), and venous thrombosis (2%). Only 1 patient with acute myelocytic leukemia had leukostasis-associated hemorrhage (white blood cells 150.1×10^3 cells/mm³), and this patient was also moderately thrombocytopenic. Etiology was multifactorial in 33% of patients and most commonly was due to the combination of ITH and coagulopathy (n = 44, 21%). ITH occurred in isolation in 44% of patients with solid tumors and 47% of those with primary brain tumors. Conversely, patients with hematopoietic tumors were more apt to hemorrhage from coagulopathy in isolation (46%) or coagulopathy in conjunction with other, less frequent diagnoses (33%), such as trauma. SAH was multifactorial in 30% of cases and was most commonly due to coagulopathy (n = 30), trauma (n = 10), or ITH (n = 6); aneurysmal SAH was rare (n = 4).

Treatment. Steroids were administered to 156 patients (75%). Reversal of coagulopathy and prevention of hematoma expansion were attempted with platelet transfusion (29%), fresh-frozen plasma or cryoprecipitate infusion (21%), or vitamin K administration (19%). Craniotomy for ventriculostomy or resection was performed in 55 patients (26%), whereas emergency therapy for increased ICP was administered to 26 (13%). Forty-six percent of patients were treated with anticonvulsants, though many were already taking seizure medications before their hemorrhage. Forty-eight patients (23%) were ultimately treated with cranial irradiation.

Outcome. At the time of statistical analysis, only 11% of patients were alive. At discharge, 15% of patients were completely independent, 33% were partially independent, 30% were completely dependent, and 22% were dead. Patients with solid tumors had the best functional outcome at discharge, with 53% being completely or partially independent, compared with 44% of patients with primary brain tumors and 30% of patients with hematologic tumors. Patients with hematopoietic tumors had the highest rate of death during hospitalization (36%), whereas patients with primary brain tumors (8%) had the lowest. Thirty-day mortality was 31% and 1-year mortality was 78% for the entire cohort. Median survival for all patients was 3 months (95% confidence interval 2–4). A difference ($p = 0.05$) in survival existed among tumor subtypes, with median survival being 5.9 months for patients with primary brain tumors, 2.1 months for patients with solid tumors, and 1.5 months for patients with hematologic tumors (figure). Median survival also varied based on etiology of hemorrhage and was 3.7 months for patients with

Figure Survival curves by tumor type and cause of intracranial hemorrhage

(A) Kaplan-Meier curve demonstrating survival by tumor type. Tumors were categorized as solid, liquid, or primary brain. A significant difference in survival exists between curves ($p = 0.05$). (B) Overall survival stratified by etiology of intracranial hemorrhage. Causes of hemorrhage were grouped as intratumoral hemorrhage, coagulopathy, both intratumoral hemorrhage and coagulopathy, or other diagnoses. A significant difference in survival exists between curves ($p = 0.009$).

ITH, 0.3 months for patients with coagulopathy, 1.8 months for patients with both ITH and coagulopathy, and 3.9 months for patients with other diagnoses ($p = 0.009$). The most common dispositions excluding death were home (50%), hospice (10%), acute rehabilitation (6%), subacute rehabilitation (5%), and transfer to another hospital (3%).

In the multivariate models, impaired consciousness, not having a primary brain tumor, multiple foci of hemorrhage, hydrocephalus, increased ICP treatment, and not receiving ventriculostomy were significant predictors of 30-day mortality (table 4). All of these variables, except not having a primary brain tumor, were also independently predictive of 90-day mortality. Additionally, hemiparesis and current chemotherapy were

significant predictors of mortality at 90 but not 30 days via multivariate analysis. Neither anticoagulant nor antiplatelet use was a significant predictor of mortality.

DISCUSSION Cancer is an important and common cause of IH. Clinical and autopsy studies have found that brain tumors represent 0.9% to 11% of spontaneous IH.^{2,7,11,16-22} The largest autopsy study of IH in patients with cancer was performed at MSKCC from 1970 to 1981 and identified 244 patients, 57% of whom were symptomatic.¹ Coagulopathy occurred in 57% of those with ICH, and 89% of these patients had hematologic malignancies, particularly leukemia (78%). ITH occurred in 38% of patients and was the second most common cause of ICH; all but 2 of these patients had a solid tumor, with melanoma and germ cell tumors being the most frequent. Hypertension was responsible for only 8% of parenchymal hemorrhages in this cohort.

Our report represents the largest clinical series of IH in patients with cancer. Systemic solid tumors were the most common underlying cancer, which differs from many previous studies where primary brain tumors accounted for the majority of malignancies.^{13,21,23,24} In one series of 110 patients with bleeding cerebral neoplasms, 77% had primary brain tumors and 23% had metastatic solid tumors.²¹ Similarly, 62% of patients with ITH in a different cohort of 58 cases had primary brain tumors.¹³ This changing demographic may represent longer survival of patients with solid tumors or the higher likelihood of primary brain tumors with IH to be clinically silent and thus not lead to acute neuroimaging.

Table 4 Predictors of 30- and 90-day mortality via multivariate logistic regression models^a

Variable	30-Day mortality	90-Day mortality
Impaired consciousness	3.1 (1.7-5.8, 0.0003)	NS
Hemiparesis	NS	2.6 (1.3-5.0, 0.006)
Recent chemotherapy	NS	2.6 (1.3-4.9, 0.004)
Primary brain tumor	0.2 (0.0-0.7, 0.02)	NS
Multiple foci of hemorrhage	2.9 (1.4-5.9, 0.004)	3.9 (2.0-7.6, <0.0001)
Hydrocephalus	3.9 (1.4-11.0, 0.009)	3.5 (1.3-9.2, 0.01)
Increased ICP treatment	3.2 (1.0-12.1, 0.06)	3.2 (1.0-10.5, 0.06)
Ventriculostomy	0.1 (0.0-0.3, 0.0001)	0.2 (0.1-0.4, <0.0001)

Abbreviations: ICP = intracranial pressure; NS = not significant.

^aVariables that did not reach statistical significance based on preset α values are not listed. Data are expressed as odds ratio (95% confidence interval, p value).

The frequency of hemorrhage into intracranial neoplasms ranges from 1.3% to 14.6% and varies markedly depending on the pathology of the underlying cancer.^{4,7,11,12,19,21,25-27} Malignant and hypervascular neoplasms have the highest predilection for hemorrhage.^{12,25,26,28,29} Factors favoring hemorrhage include overexpression of vascular endothelial growth factor and matrix metalloproteinases, imbalances in the fibrinolytic cascade, retiform type capillaries, rapid tumor growth, vascular invasion, tumor necrosis, and neovascularization.³⁰⁻³³ Melanoma, lung, glioma, breast, and leukemia were the most common tumor types in our cohort. The high rates of hemorrhage in patients with breast and prostate cancer were unexpected. Alternatively, we saw low rates of hemorrhage in patients with renal, germ cell, thyroid, and hepatocellular carcinomas previously thought to be highly associated with ITH.

ITH, coagulopathy, or the combination of the 2 accounted for the majority of IH. Hypertension, amyloid angiopathy, and other common causes of IH in the general population were rare, highlighting the unique pathophysiology of IH in patients with cancer. Patients with solid or primary brain tumors most often bled from ITH, whereas patients with hematopoietic tumors most often bled from coagulopathy. Patients with hematologic malignancies were also most likely to bleed from the rarer etiologies in our cohort, such as trauma or hemorrhagic conversion of stroke. Previous studies had found hyperleukocytosis and DIC to be common causes of IH in acute leukemia,^{1,3,34,35} but both syndromes were rare in our series, reflecting the advances in therapy and changing natural history of acute leukemia.

Anticoagulation of patients with primary or metastatic brain tumors and thromboembolism is often avoided for fear of catastrophic IH despite existing data suggesting that the risk is small.^{36,37} One retrospective study of 42 patients with cerebral metastases on therapeutic anticoagulation found only 3 symptomatic ITHs, 2 of which occurred in the setting of supratherapeutic values.³⁶ Nineteen percent of our patients were on therapeutic anticoagulation at the time of hemorrhage, and only 3% were supratherapeutic. There was no significant association between anticoagulation and mortality, supporting the safety of this treatment in hypercoagulable cancer patients. This holds true for patients with primary or metastatic brain tumors, because nearly half of our patients had known brain lesions before IH. Furthermore, antiangiogenic therapies were not associated with a substantial risk of ITH. This was also observed in a recent study of 21 patients with glioma receiving concurrent bevacizumab and anticoagulation, none of whom developed severe IH.³⁷

Patients with cancer have a poor overall prognosis after IH. Median survival was 3 months, and only 22% of patients lived 1 year. Despite short survival, many patients had excellent functional outcomes, and nearly half were completely or partially independent at the time of discharge. Half of our cohort was also discharged home. Mortality at 30 days (31%) was similar to that of ICH in the general population and only began to worsen compared with historic controls as time from hemorrhage advanced.^{38,39} This trend suggests that many patients died from their systemic malignancy and not from the hemorrhage itself. Patients with primary brain tumors had the best prognosis, with a median survival of 5.9 months. These patients lived a median of 12.3 months from diagnosis, comparable to the typical life span of patients with malignant brain tumors. Patients with hematopoietic tumors had the worst prognosis, with more than a third dying during hospitalization. This can be attributed to their high rate of coagulopathy, which in isolation was associated with a median survival of only 0.3 months. These patients typically had severe coagulopathy and would develop refractory hemorrhage into multiple cerebral compartments.

Poor prognostic indicators were impaired consciousness, hemiparesis, multiple hemorrhagic foci, hydrocephalus, and treatment for increased ICP (table 4). Recent chemotherapy, not having a primary brain tumor, and lack of ventriculostomy also predicted poor outcome. Recent chemotherapy likely indicates patients with more aggressive disease and higher rates of pancytopenia. Not receiving a ventriculostomy may identify patients treated less aggressively. Steroid administration was common in our IH cohort (75%) and correlated with the rate of ITH (61%). Glucocorticoids were used to suppress tumor-associated edema and promote oncolysis in some hematologic malignancies; its use did not affect outcome (30-day mortality odds ratio 0.8, $p = 0.45$).

There are several limitations to our study, most importantly its retrospective nature. We did not address isolated subdural or epidural hematomas. Subdural hemorrhage in patients with cancer is often associated with bone and dural metastases and has a different course and outcome from ITHs.⁴⁰ Epidural hematomas were not included as most are postoperative at our institution. Our study also excluded outpatient hemorrhages because we had no comprehensive method of ascertainment. Hemorrhages recognized in outpatients are more likely to be asymptomatic or mildly symptomatic and unlikely to affect morbidity or mortality. Our median survival would probably improve if these hemorrhages were included. Last, MSKCC is not a designated stroke center. Some patients were likely taken to nearby stroke centers, poten-

tially decreasing the number of larger and more disabling hemorrhages.

This study describes the unique pathophysiology and outcome of patients with cancer and IH. ITH and coagulopathy cause most ITHs in patients with cancer, whereas hypertension and other causes typical in the general community are rare. Changes in etiology of IH in patients with cancer parallel improvements in management of the underlying neoplasm, particularly in the hematologic malignancies. Prognosis is generally poor, although many patients retain independence after IH and ultimately succumb to their underlying malignancy and not the hemorrhage itself.

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by Anne S. Reiner, MPH, and Katherine S. Panageas, DrPH.

DISCLOSURE

Dr. Navi, Dr. Reichman, Dr. Berlin, Ms. Reiner, and Dr. Panageas report no disclosures. Dr. Segal serves on the speakers' bureau for Boehringer Ingelheim. Dr. DeAngelis has served on a scientific advisory board for Genentech Inc.; serves on the editorial board of *Neurology*; receives publishing royalties for *The Neurologic Complications of Cancer* (Oxford University Press, 2008); and has received research support from the NIH (UO1 CA-105663-01 [Participating Member in the NABTC]).

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CDC, AAN to Health Care Professionals: Monitor Patients for GBS

The Centers for Disease Control and Prevention (CDC) and the American Academy of Neurology (AAN) collaborated to reach out to neurologists across the US to monitor and report any possible new cases of Guillain-Barré syndrome (GBS) following 2009 H1N1 flu vaccination.

Neurologists and health care professionals nationwide who diagnose patients with vaccine-associated GBS should use the CDC and FDA Vaccine Adverse Event Reporting System (VAERS) to report their observations.

In addition, neurologists and all health practitioners in the 10 Emerging Infections Program (EIP) states—California, Connecticut, Maryland, Minnesota, New Mexico, New York, Colorado, Oregon, Georgia, and Tennessee—are asked to report all new cases of GBS, regardless of vaccination status, to their state's surveillance officer.

The AAN hosted a series of webinars providing an in-depth look at H1N1 vaccination and how it may pose a risk for GBS and information about the vaccination monitoring campaign.

For additional information about the monitoring campaign, or to watch the webinars or download VAERS form and information on reporting to surveillance officers in your state, visit the AAN's GBS toolkit page, www.aan.com/view/gbstoolkit.