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Intracranial Hemorrhage in Patients with Cancer

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Abstract Intracranial hemorrhage (ICH) is a common neurological emergency in patients with cancer, typically occurring late in the disease course, although it occasionally heralds the cancer diagnosis. ICH in these patients often occurs from unique mechanisms, especially intratumoral hemorrhage or coagulopathy, whereas hypertensive hemorrhage is rare. Lung, melanoma, breast, and glioblastoma multiforme are the most commonly associated solid tumors, partly because of their ubiquity and frequent brain involvement, whereas leukemia is the most commonly associated hematological cancer. Patients typically present with focal neurological deficits, headache, and encephalopathy, and their initial diagnostic evaluation and management should follow standard guidelines, although steroids and/or surgical resection should be strongly considered in those with intratumoral hemorrhage. Short-term outcomes are comparable to ICH in the community, whereas long-term outcomes are generally poor, corresponding to the prognosis of the underlying cancer. This review focuses on the recent advances and special considerations in cancer-related intracranial hemorrhage.

Keywords Cancer · Malignancy · Neoplasm · Intracranial hemorrhage · Hemorrhagic stroke · Intracerebral hemorrhage · Subarachnoid hemorrhage

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Introduction

Intracranial hemorrhage (ICH) is a highly morbid neurological disease that accounts for nearly half the cerebrovascular events in patients with cancer [1, 2]. ICH in these patients may result directly from hemorrhage into a brain tumor or indirectly from systemic effects of oncological therapy. Knowledge of the relationship between cancer and ICH is important, as the presentation, management, and outcome of ICH in patients with cancer differs from the general population, and ICH in these patients often alters further oncological therapy and goals of care.

Types and Mechanisms

Cancer is associated with hemorrhage into all compartments of the brain, although intraparenchymal hemorrhage (IPH; ie, bleeding confined to brain tissue) is the most common, followed by subdural hemorrhage (SDH), subarachnoid hemorrhage (SAH), and epidural hemorrhage (EDH), respectively (Table 1) [2]. The most frequent reasons for symptomatic ICH are intratumoral hemorrhage and coagulopathy [2–5••]. Hemorrhagic brain tumors can cause IPH, SAH, or intraventricular hemorrhage depending on their

Table 1 Pathophysiology of intracranial hemorrhage in patients with cancer

Etiology	Location(s)	Mechanism(s)	Tumor(s)	Association(s)
Intratumoral hemorrhage	IPH SAH SDH EDH	Tumor cell necrosis, neoangiogenesis, and blood vessel invasion	Lung Melanoma Breast Renal cell Thyroid Choriocarcinoma Hepatocellular Glioblastoma Oligodendroglioma	XRT Concomitant coagulopathy
Coagulopathy	IPH SAH SDH	Dysfunction or deficiency of clotting factors or platelets	Hematological malignancies (especially APML)	Bone marrow dysfunction Liver disease Vitamin K deficiency DIC Chemotherapy XRT Sepsis
Venous sinus thrombosis	IPH SAH	Hypercoagulable state Neoplastic compression of venous sinus	Leukemia Metastatic solid tumors Meningioma	L-asparaginase
Hypertension	IPH	End arteriole lipohyalinosis	No specific cancer predilection	VEGF inhibitors
Trauma	IPH SAH SDH EDH	Shearing or tearing of veins or arteries	No specific cancer predilection	Concomitant coagulopathy
Hemorrhagic conversion of an ischemic stroke	IPH	Reperfusion injury	Mucinous adenocarcinomas	Endocarditis Cardioembolic strokes
PRES	IPH SAH	Impaired autoregulation	No specific cancer predilection	Hypertension Renal impairment Calcineurin inhibitors VEGF inhibitors Cisplatin
Aneurysm	IPH SAH	Saccular, neoplastic, or mycotic aneurysm	Choriocarcinoma Cardiac myxoma Lung	Bacterial or fungal endocarditis
Hyperleukocytosis	IPH	Vascular sludging and occlusion	Acute leukemia	WBC >100,000 cells/mm^3

APML acute promyelocytic leukemia; *DIC* disseminated intravascular coagulation; *EDH* epidural hemorrhage; *IPH* intraparenchymal hemorrhage; *PRES* posterior reversible encephalopathy syndrome; *SAH* subarachnoid hemorrhage; *SDH* subdural hemorrhage; *VEGF* vascular endothelial growth factor; *XRT* radiation therapy; *WBC* white blood cells

location [2, 5••, 6], whereas dural- or skull-based tumors, most commonly metastases from the stomach, prostate, or breast, can cause SDH or EDH [2, 6–9].

Coagulopathy typically arises from multiple mechanisms, including abnormalities of platelets, coagulation factors, or both. Thrombocytopenia often occurs from bone marrow suppression secondary to chemotherapy or radiation, tumor infiltration, or intrinsic failure (in hematological malignancies) [10]. Impairments of the coagulation cascade generally result from liver failure, vitamin K deficiency due to poor nutrition, or disseminated intravascular coagulation (DIC) [2, 10]. Patients receiving bone marrow transplantation are particularly susceptible to sepsis and resultant DIC [10]. Intrinsic promyelocytic degranulation in patients with acute promyelocytic leukemia resulting in florid DIC at presentation has been largely eliminated with the incorporation of all-transretinoic acid in the initial therapeutic regimen.

Less frequent causes of ICH in patients with cancer include hemorrhagic conversion of ischemic stroke, venous sinus thrombosis (either from hypercoagulability or neoplastic venous sinus compression), hypertension, posterior reversible encephalopathy syndrome, and trauma [2, 5••, 6, 7]. Rare causes unique to patients with cancer include leukostasis and hyperviscosity [10].

Incidence

Cancer in Patients with Intracranial Hemorrhage

Hemorrhage into primary or metastatic brain tumors account for a small proportion of spontaneous ICH, although the exact incidence is unclear, as different series have reported widely varying results. Some studies suggest as few as 1 % to 2 % of spontaneous ICH are due to an underlying cancer [11, 12•], whereas others report rates as high as 7 % to 10 % [3, 13, 14], with primary brain tumors and metastases accounting for nearly equal proportion of cases across series.

ICH is a late complication of cancer in most patients, but it may rarely precede the cancer diagnosis. The incidence of cancer presenting as ICH is variable depending on the patient population studied. In surgical series of ICH, brain hemorrhage was the presenting symptom of cancer in 3 of 54 (6 %) and 3 of 80 (4 %) cases [15, 16]; whereas in a large autopsy series of ICH, an underlying and unsuspected cancer was discovered in only 4 of 430 (1 %) cases [13]. Furthermore, in the largest neuroimaging series to date, 29 of 692 (4 %) cases of ICH first detected by head computed tomography (CT) were attributed to an unsuspected brain tumor [14].

Intracranial Hemorrhage in Patients with Cancer

Older, predominantly histologic series report rates of ICH in patients with systemic or brain neoplasms of 2 % to 14 % [2, 4, 14, 17–19], compared to 25 IPH per 100,000 patient-years in the general population as noted in a recent meta-analysis [20].

Several tumors, particularly malignant ones, have an increased predilection for intratumoral hemorrhage (Table 1) [2, 4, 5••, 14, 18, 21]. Of primary brain tumors, glioblastoma multiforme is most frequently associated with ICH, because it is the most common primary brain tumor and because its tumor cells are highly invasive and destructive [4, 14, 18, 21] (Table 2). Oligodendrogliomas, though much less frequent neoplasms, are also predisposed to hemorrhage even when low grade because they contain fragile retiform capillaries [22]. Similarly, benign neoplasms, particularly meningiomas, can also cause intratumoral hemorrhage; benign neoplasms accounted for 23 of 110 (21 %) and 9 of 50 (18 %) cases of intratumoral hemorrhage in two clinical series [4, 14].

Lung, melanoma, breast, and renal cell cancers are the most common systemic solid tumors associated with ICH [5••]. Their frequent association with ICH is partly explained by their ubiquity—these tumors have a high incidence in the population and account for most brain metastases—and their histological composition, which has elements of neoangiogenesis, tumor cell necrosis, and parenchymal blood vessel invasion [19, 23, 24]. Conversely, thyroid cancer, hepatocellular carcinoma, and choriocarcinoma are rare causes of brain metastases, but have an unusually high predisposition to hemorrhage, accounting for their overrepresentation of ICH in cancer series [2, 19, 25]. For instance, 19 of 244 (8 %) patients had choriocarcinoma in a large autopsy series of patients with cancer and ICH [2]. In addition, although prostate cancer rarely metastasizes to the brain, it accounted for a sizeable proportion (5 %) of ICH in a recent clinical series of patients with cancer [5••]. This increased incidence compared to prior reports may be due to improvements in prostate cancer therapy, which may have altered the natural history of disease allowing for longer survival and increased risk of cerebrovascular complications.

Hematological malignancies, particularly leukemia, are also a frequent cause of ICH. These tumors generally cause ICH through coagulopathy from severe thrombocytopenia or coagulation cascade dysfunction [2, 3, 5••]. For instance, one study reported a mean platelet count of 13,500/mm^3 in patients with leukemia (without intracranial invasion) and ICH [2]. However, lymphomas and leukemias can rarely metastasize to the brain parenchyma or arachnoid mater and cause brain hemorrhage; although even with leukemic infiltration of the parenchyma, ICH typically occurs only in the setting of severe coagulopathy—the mean platelet count was about 36,000/mm^3 in the series reported by Graus et al. [2].

Table 2 Specific tumors associated with intracranial hemorrhage in large series[a]

	Navi et al. [5••] / 2010 (n=208)	Licata and Turazzi [3] / 2003 (n=105)[b]	Liu et al. [21] / 2002 (n=52)[b]	Schrader et al. [14] / 2000 (n=49)[c]	Kondziolka et al. [18] / 1987 (n=49)[d]	Graus et al. [2] / 1985 (n=244)[e]
Solid tumors, %[f]	68	24	42	37	22	47
Melanoma	15	2	2	16	10	9
Lung	14	–	29	4	–	3
Breast	7	–	2	–	–	0
Prostate	5	–	–	–	–	–
Renal	4	–	–	4	–	1
Colorectal	3	–	–	–	–	–
Thyroid	1	–	–	2	–	–
Hepatocellular	–	–	8	–	–	–
Testicular	2	–	–	–	–	–
Germ cell	–	–	2	2	–	8
Sarcoma	–	–	–	2	4	2
Other or unspecified	17	22	–	6	8	24
Liquid tumors, %	16	–	–	2	2	52
Leukemia	6	–	–	–	–	45
Lymphoma	4	–	–	–	2	6
Multiple myeloma	–	–	–	–	–	1
MDS	2	–	–	–	–	–
Other	3	–	–	2	–	–
Primary brain tumors, %	16	76	58	61	76	–
Glioma	12	60	33	47	71	–
GBM	7	34	19	31	35	–
Oligodendroglioma	3	–	6	4	4	–
Astrocytoma	2	–	7	12	18	–
Other or mixed glioma	–	26	–	–	14	–
Ependymoma	–	–	2	4	–	–
PCNSL	2	–	–	–	–	–
Meningioma	2	12	19	4	2	–
Hemangioblastoma	–	2	–	–	–	–
Neuroblastoma	–	1	–	–	–	–
Medulloblastoma	–	–	–	–	–	–
Pinealoblastoma	–	1	–	–	–	–
Other	1	–	4	6	2	–
Unknown/unspecified, %	–	–	–	–	–	1

[a] Table includes only English-language series with >45 cases

[b] Table excludes pituitary adenomas

[c] Table excludes 1 tuberculoma

[d] Table includes macroscopic hemorrhage only

[e] Study excluded primary brain tumors

[f] Percentages are rounded to the nearest integer and may not add to 100 %

GBM glioblastoma multiforme; *MDS* myelodysplastic syndrome; *PCNSL* primary central nervous system lymphoma

Biological Mechanisms

The biology of ICH in patients with cancer primarily relates to intratumoral hemorrhage as a consequence of central nervous system (CNS) metastases, which is explained in part by the "seed and soil" hypothesis first proposed over 100 years ago by the pathologist Paget [26]. Brain metastases typically arise from hematogenous spread of tumor cells to CNS capillary beds. These invasive tumor cells have usually already metastasized to (or originated from) the lung, allowing access to the arterial circulation. Upon lodging in the distal capillary beds with a predilection for the watershed areas, tumor cells extravasate from the circulation and

invade the normal brain parenchyma; those (ie, the "seed") that find the CNS environment (ie, the "soil") hospitable proliferate and ultimately form brain metastases. Brain metastases and their resultant intratumoral hemorrhages are usually supratentorial because the anterior circulation provides 80 % of cerebral blood flow. The seed and soil hypothesis can explain the propensity of certain tumors (eg, melanoma) to establish brain metastases.

The factors leading to intratumoral hemorrhage are less clear. Imbalances in the fibrinolytic cascade, overexpression of vascular endothelial growth factor and metalloproteinases, and aberrant neovascularization are a few suspected mechanisms [27, 28]. Additionally, coagulopathy, trauma, and a higher pathological grade may increase the risk of hemorrhage for any given tumor type [2, 5••].

Clinical Characteristics and Etiology

Patients with cancer who develop ICH are generally symptomatic when diagnosed radiographically (94 %) [5••]; however, patients identified at autopsy or surgery may not be [2, 29]. The presentation of ICH in patients with cancer largely parallels its presentation in the general population. Common symptoms or signs include hemiparesis (48 %), headache (41 %), encephalopathy (18 %), nausea or vomiting (18 %), seizure (17 %), and coma (6 %) [5••]. Occasionally, symptoms may be nonspecific and gradual, characterized by confusion or lethargy (64 % of patients with SDH in one series) [2].

ICH in patients with cancer is often caused by unique mechanisms not seen in the general population. The largest modern clinical series of 208 cancer patients with IPH or SAH reported that 61 % (n=127) of cases were caused by intratumoral hemorrhage and 46 % (n=95) by coagulopathy; 33 % (n=69) had multifactorial causes and 21 % (n=44) had both intratumoral hemorrhage and coagulopathy [5••]. Coagulopathy was usually caused by thrombocytopenia (platelet counts <50,000/mm^3; n=40) or an INR >1.5 (n=28); four patients had documented DIC, two of whom had acute promyelocytic leukemia [5]. Not surprisingly, ICH was usually caused by intratumoral hemorrhage in patients with solid tumors and coagulopathy in patients with hematological malignancies. Less frequent etiologies were trauma (6 %, n=12), hemorrhagic conversion of ischemic stroke (4 %, n=8), venous thrombosis (2 %, n=5), and aneurysmal rupture (2 %, n=4); one patient had a leukostasis-associated hemorrhage, which can occur in patients with leukemia when peripheral white blood cell counts rise above 100,000 cells/mm^3 [5••]. Interestingly, hypertension, which is the most common cause of IPH in the community, only caused 5 % (n=11) of ICH in this series [5••].

Though primarily intraparenchymal, ICH in patients with cancer often involves multiple intracranial compartments [2, 4, 5••, 21, 29]. SAH and intraventricular hemorrhage may occur, usually from coagulopathy, trauma, or intratumoral hemorrhage, and not from arteriovenous malformations or aneurysms (only 9 % in one large series) [5••]. However, when aneurysmal SAHs do occur in patients with cancer, an evaluation for atypical causes of aneurysms—mycotic and neoplastic—may be necessary. Neoplastic and mycotic aneurysms are fusiform, typically develop in distal middle cerebral artery branches, and are most commonly associated with atrial myxoma, choriocarcinoma, and lung carcinoma [6, 10].

SDH commonly occurs in patients with cancer, and usually results from coagulopathy or trauma, although recent craniotomy or lumbar puncture and intratumoral hemorrhage from dura mater metastases are alternative causes [7, 8, 30]. Interestingly, only 15 % to 40 % of patients with dural metastases have a coexistent SDH [8]. EDH usually results from trauma or coagulopathy, but in rare cases may occur from calvarial or dural neoplasms (primary or metastatic) [10, 31]. Intraspinal hematoma is rare, but may occur after lumbar puncture in a patient with severe coagulopathy [2].

Diagnostic Evaluation

Patients with cancer and a suspected ICH should be evaluated initially with a non-contrast head CT because of its speed, availability, and sensitivity for acute blood. If no contraindications are present (eg, renal insufficiency or iodinated contrast allergy), post-contrast sequences and CT angiography may also help assess for underlying tumor and vascular malformations. Additionally, a "spot sign" may be seen on post-contrast sequences, indicating active bleeding and predicting hematoma expansion [32]. Laboratory evaluation should assess for coagulopathy with a complete blood count, coagulation profile, and a DIC panel (eg, D-dimer and fibrinogen levels). If DIC is suspected, a peripheral blood smear should be performed to evaluate for schistocytes.

Once the patient is stable, brain magnetic resonance imaging (MRI) with contrast should be performed to evaluate for an underlying tumor. Multifocal hemorrhages, perihematomal enhancement, additional enhancing foci, and hematoma at the gray-white junction are all suggestive of an underlying cancer [10, 33]. Excessive edema surrounding the hematoma on immediate neuroimaging is often a clue to an underlying neoplasm; one study reported a positive predictive value of 71 % for underlying metastases if the vasogenic edema to mean hematoma diameter ratio was greater than 100 % [34]. Additionally, delayed hematoma evolution, persistent edema, and diminished or absent hemosiderin deposition on convalescent imaging are also suspicious

for intratumoral hemorrhage [33]. MRI also optimally evaluates for alternate etiologies, including ischemic stroke with hemorrhagic conversion (via diffusion weighted imaging), venous sinus thrombosis (thrombosed veins demonstrate flow voids on pre-contrast images and restricted enhancement on post-contrast images), and amyloid angiopathy (lobar microhemorrhages on susceptibility weighted sequences).

Management

The management of acute ICH in patients with cancer should conform to established guidelines for IPH, SAH, SDH, and EDH, with the following qualifications detailed below [1, 35, 36]. In patients with intratumoral hemorrhage, steroids should be used to decrease mass effect from vasogenic edema [5••], and the underlying tumor should be considered for resection if surgically feasible [4, 5••, 14, 21]. The proven survival benefit of surgical resection in patients with primary brain tumors or solitary or few brain metastases [37], the immediate improvement in mass effect, and the lobar location of most intratumoral hemorrhages supports these different practice patterns; surgeons may be more inclined to operate on lobar hemorrhages because there was a non-significant trend towards improved outcomes in patients with lobar IPH randomized to surgery in the International Surgical Trial in Intracerebral Hemorrhage [38]. In patients with unresectable tumors or those with more than three metastatic lesions, whole brain radiation may be considered instead as a palliative measure.

In patients with ICH from a bleeding diathesis, treatment should be aimed at correcting the coagulopathy. If thrombocytopenia or qualitative platelet dysfunction exists, platelet transfusions should be administered with a goal platelet value of $\geq$70,000/mm^3. Patients with elevated prothrombin or partial thromboplastin times should be treated with intravenous vitamin K and fresh frozen plasma. Patients whose coagulopathy is secondary to anticoagulants should be considered for prothrombin complex concentrate, although there are no clinical trials to support this practice and prothrombin complex concentrate may increase the risk of systemic thrombosis, particularly in hypercoagulable cancer patients [1]. Recombinant factor VIIa should not be administered to patients with cancer and ICH as its use in patients with acute IPH is associated with increased thrombotic complications and no survival benefit [1, 39]. DIC treatment should aim to suppress the underlying etiology (eg, sepsis) and replace coagulation factors.

Patients with cancer who develop acute SAH from saccular cerebral aneurysms or arteriovenous malformations should be treated in the standard fashion with neurosurgical or endovascular therapy, and any complications of SAH, such as vasospasm and hydrocephalus, should follow standard therapeutic guidelines. However, SAH from neoplastic or mycotic aneurysms are typically distal, fusiform, and not easily amenable to surgery or endovascular coiling [10]. For these reasons and because of their underlying pathophysiology, neoplastic aneurysms are usually treated with brain radiation or chemotherapy, whereas mycotic aneurysms are typically treated with antibiotics [10]. The management of acute SDH and EDH in patients with cancer does not differ significantly from the general population; patients with these conditions should be surgically decompressed if indicated clinically.

Outcomes

The short-term prognosis of ICH in patients with cancer is comparable to those without cancer. Modern clinical series report 22 % to 31 % mortality at 1 month, and 48 % to 75 % partial or complete independence at discharge or 1 month [4, 5••, 14]. However, long-term outcomes are governed by the prognosis of the underlying malignancy and are often poor (78 % mortality at 1 year), as ICH generally occurs late in the neoplastic course [5••]. Patients with ICH from coagulopathy fare worse than patients with ICH from intratumoral hemorrhage, likely because of larger hemorrhages into multiple intracranial compartments and more severe acute illness [5••]. Predictors of poor prognosis in patients with cancer and ICH include an underlying systemic malignancy (ie, not a primary brain tumor), multiple hemorrhagic foci, hydrocephalus, treatment for increased intracranial pressure (likely reflecting more severe disease), and absence of ventriculostomy [5••]. Preceding anticoagulant or antiplatelet use does not significantly affect mortality [5••].

Special Considerations

Screening Patients with Idiopathic Intraparenchymal Hemorrhage for Cancer

As cancer can present with IPH, physicians should consider screening for an underlying neoplasm, particularly if the patient lacks typical risk factors for IPH, or the hemorrhage is multifocal, at the gray-white junction, or associated with an unexpected degree of surrounding edema. A thorough history and physical examination, including a total body skin check, is imperative. Patients should be assessed carefully for a history of gradual neurological symptoms, smoking, weight loss, constitutional symptoms, and remote malignancy. Additionally, recent chest X-rays should be inspected for pulmonary or osseous lesions, as metastases rarely reach the brain without pulmonary involvement.

The timing and indication for contrast-enhanced brain MRI in the diagnostic evaluation of idiopathic IPH is more controversial because of its high cost and unclear diagnostic yield. In one study of 148 patients with unexplained IPH evaluated with brain MRI, only one patient was found to have an underlying tumor [12•]. Furthermore, acute IPH may obscure an underlying tumor, resulting in a false-negative study if MRI is performed too early [40]. Therefore, unless there is a high suspicion for cancer or another cause of IPH frequently detected on MRI such as amyloid angiopathy or hemorrhagic conversion of an ischemic stroke, we recommend performing MRI 1 to 3 months after the ictus to maximize diagnostic yield.

Risk of Thrombolysis in Patients with Intracranial Neoplasms

Intravenous thrombolysis for acute stroke is generally not considered in patients with known intracranial neoplasms because stroke mimics (eg, seizures) are common in these patients and there is considerable risk for inducing intratumoral hemorrhage. There are few reports in the literature of patients with intracranial neoplasms receiving thrombolysis—two patients with meningioma, two with glioblastoma multiforme, and one with vestibular schwannoma [41]. Of these cases, only one patient with a previously undiagnosed glioblastoma multiforme developed symptomatic intratumoral hemorrhage; however, reports of hemorrhage into brain tumors after thrombolysis may be limited by publication bias. Conversely, intravenous thrombolysis for acute stroke appeared safe in two studies of patients with systemic cancer and no known CNS involvement [42•, 43]. As the safety of intravenous thrombolysis in patients with intracranial neoplasms and acute stroke is unclear, we recommend intra-arterial thrombolysis or mechanical thrombectomy in appropriate patients (eg, those with proximal large artery strokes), as these techniques may be associated with a decreased risk of symptomatic hemorrhage.

Safety of Anticoagulation in Patients with Intracranial Neoplasms

Therapeutic anticoagulation for systemic thromboembolism appears safe in patients with primary or metastatic brain tumors [5••, 44]. In patients with brain metastases receiving therapeutic anticoagulation, only 3 of 42 (7 %) suffered symptomatic ICH, two of whom were supra-therapeutic [44]. Similarly, only one symptomatic and two asymptomatic hemorrhages occurred in 21 patients with gliomas treated with bevacizumab on anticoagulation [45]. In the largest modern series of IPH and SAH in patients with cancer, anticoagulation (19 % of cohort) was not associated with increased mortality [5••]. As an untreated pulmonary embolism frequently causes death in patients with cancer, and the risk of ICH in patients with intracranial neoplasms receiving anticoagulation does not appear to be increased, we recommend therapeutic anticoagulation for patients with intracranial neoplasms and acute venous thromboembolism. However, if a patient with cancer and symptomatic ICH develops an acute deep vein or pulmonary thromboembolism, anticoagulation should be avoided and a removable inferior vena cava filter inserted to prevent propagation of thrombus; once the patient has recovered from the ICH, the filter may be removed and anticoagulants instituted if the risk of recurrent hemorrhage is low. In patients with brain tumors and atrial fibrillation or other indications for therapeutic anticoagulation, most can be anticoagulated safely but treatment should be tailored to account for individualized risks of treatment.

Association of Chemotherapy and Radiation with Intracranial Hemorrhage

Chemotherapy-induced bone marrow suppression and resultant coagulopathy is a common cause of ICH in patients with cancer. Additionally, several chemotherapeutic agents may cause ICH through unique mechanisms. For instance, L-asparaginase in children with acute lymphoblastic leukemia reduces levels of antithrombin III, protein C, fibrinogen, and plasminogen, occasionally leading to venous sinus thrombosis and subsequent IPH [6]. Among newer chemotherapeutic agents, anti-angiogenic drugs targeting vascular endothelial growth factor may increase the risk of ICH. Bevacizumab was associated with ICH in a patient with hepatocellular carcinoma in an early clinical trial, but a recent study has contested this association, reporting similar rates of ICH in patients with systemic cancer or glioblastoma treated with bevacizumab compared to similar patients not receiving the drug [46•]. Sunitinib has also been associated with ICH in patients with renal cell carcinoma and glioma, but appeared safe in a recent series of patients with brain metastases from non-small cell lung cancer [47].

Radiation predisposes to the delayed development of vascular malformations, particularly cavernous hemangiomas, which may cause ICH [6]. Radiation may also precipitate hemorrhage into intracranial tumors, although the data for this are conflicting [48].

Conclusions

ICH of all forms occurs commonly in patients with cancer, often arising from unique mechanisms not encountered in the general population. As many hemorrhages are related to intrinsic properties of the neoplasm or its treatment, careful attention should be paid to cancer stage, histology, and

recent therapy. Emergency treatment may be life-saving and should be initiated unless it contradicts known goals of care. Prognosis in the short-term is comparable to that seen in non-cancer patients, although long-term outcomes are often worse, usually corresponding to the prognosis of the underlying malignancy. Future studies are needed to determine the optimal diagnostic modality and treatment of patients with proven or suspected cancer-related ICH.

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- • Of importance
- •• Of major importance

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