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Ischemic Stroke in Cancer Patients: A Review of an Underappreciated Pathology

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Abstract

Currently one-in-ten patients with ischemic stroke have comorbid cancer and this frequency is expected to increase with continued advances in cancer therapeutics prolonging median survival. Well known for its association with venous thrombosis, cancer has recently emerged as a significant risk factor for arterial thromboembolism including stroke, however, the underlying mechanisms are uncertain. In addition, the optimal strategies to prevent and acutely treat stroke in cancer patients is yet to be established. This review summarizes the current evidence on ischemic stroke risk, biomarkers, pathophysiology, treatments, and prognosis in cancer patients, emphasizing knowledge gaps and the potential strategies to address them.

Keywords

ischemic stroke; cancer; review

Introduction

The estimated lifetime incidence of malignant cancer is 40%, and currently 13 million Americans are living with cancer.¹ While historically a devastating disease, the past few decades have seen innumerable advances in cancer diagnostics and treatments, so that now, most patients survive at least 5 years from cancer diagnosis.² In addition, further progress is expected given recent breakthroughs in cancer screening, molecular diagnostics, targeted chemotherapy, and immunotherapy.³ Therefore, long-term quality of life has become more important for cancer patients, making the prevention of diseases and cancer-related complications that hinder functional status paramount. This includes ischemic stroke—a leading cause of death and disability.⁴

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Both BBN and CI contributed to the concept and design of the study; acquisition and analysis of data; and drafting the manuscript and figures.

Potential Conflicts of Interest

Nothing to report.

Physicians have known for centuries that cancer increases venous thromboembolism risk and that most thrombotic events in cancer patients are within the venous circulation.⁵ Consequently, the medical community has invested considerable time and resources to evaluate strategies to prevent, diagnose, and treat cancer-associated venous thromboembolism.⁶ Yet, until recently, it was uncertain whether cancer also increased arterial thromboembolism risk; and therefore, cancer-associated stroke was often overlooked, with research generally limited to descriptive case series and autopsy studies.^{7, 8} However, new data from several, large-scale, analytical cohort studies have established that incident cancer is also associated with a substantially increased short-term risk of arterial thromboembolism, including ischemic stroke,^{9–12} and that cancer may increase the risk of early deterioration, disability, recurrent thromboembolism, and mortality after stroke.^{13–18} These new data have sparked a conceptual shift among physicians whereby increased attention is paid to arterial thromboembolism in cancer patients, especially as arterial events are generally more impactful than venous events.¹⁹ This increased focus is most notable among cardiologists, as evidenced by the rapidly growing subspecialty of “oncocardiology”, although neurologists also are becoming more aware of this increasingly recognized clinical problem.²⁰

Despite accumulating knowledge, many aspects of the association between cancer and stroke remain uncertain. For instance, the mechanisms responsible for cancer patients’ increased risk of stroke are unclear. Coupled with this mechanistic uncertainty is the lack of high-quality evidence regarding optimal strategies for stroke prevention and acute treatment in cancer patients. Herein, we seek to provide a critical appraisal of recently emerged data linking cancer to ischemic stroke, focusing on mechanisms, biomarkers, outcomes, management, and current knowledge gaps and potential research strategies to address them.

Epidemiology

Cancer Incidence in Stroke Patients

Cancer is the second and stroke is the fifth leading cause of death in the United States.²¹ Both diseases cause substantial disability and societal cost.²² A Nationwide Inpatient Sample study reported that 10% of hospitalized ischemic stroke patients have comorbid cancer and that this association may be on the rise.²³ Additionally, in the two years after ischemic stroke, another 3–5% of patients receive a new cancer diagnosis.^{24–26} This risk of incident, previously occult cancer appears highest in patients with cryptogenic stroke, in whom, it is conceivable that the cancer caused or triggered the stroke through hypercoagulability.²⁴ Potential biomarkers for occult cancer in stroke patients include elevated D-dimer, fibrinogen, and C-reactive protein; infarction in multiple vascular territories; and poor nutritional status.^{24–29} Most comorbid cancers in stroke patients are solid tumors of the lung, gastrointestinal tract, and breast.^{30–32} In addition, most patients with cancer and stroke are elderly and male, although patients of any age, sex, or race/ethnicity can be affected.³¹

Stroke Incidence in Cancer Patients

New diagnoses of solid or hematological cancers are associated with a substantially increased short-term risk of stroke.^{9–11} Stroke risk varies by cancer type, histology, and stage.⁹ Cancer types classically associated with venous thromboembolism, such as pancreas, gastric, and lung, seem to have the highest risks of arterial thromboembolism.^{9, 10} For example, in a Medicare claims-based study, at 1 year from cancer diagnosis, 6.9% of elderly lung cancer patients had developed ischemic stroke as compared to 3.2% of matched controls, equating to more than a doubling in risk.⁹ Stroke risk directly correlates with cancer stage, with stage 4 cancers demonstrating the highest risks, including a more than tenfold increased risk in the first month after cancer diagnosis.⁹

Clinical Presentation

The presentation of stroke in cancer patients is similar to that in the general population with notable exceptions. Most cancer patients with ischemic stroke present with hemiparesis, speech disturbance, and/or visual field changes.⁸ However, because of frequent embolic sources causing multifocal infarcts, encephalopathy is also common.²⁹ This is especially true in cancer patients whose stroke mechanism is undetermined, among whom nearly 60% demonstrate multifocal embolic-appearing infarcts.^{8, 31, 32} Concomitant venous and systemic arterial thromboembolism is also common in this population. For instance, in one study, 12% of cancer patients hospitalized with stroke had prior venous thromboembolism as compared to 1% of non-cancer patients with stroke.³³ Most cancer patients with stroke have advanced disease with known metastases, although patients with early stage cancers can also develop stroke.^{10, 31} Furthermore, stroke can sometimes be the initial manifestation of cancer.^{34–36}

Ischemic strokes tend to be more severe in cancer patients than in non-cancer patients.¹³ Furthermore, cancer patients with stroke generally have worse discharge disposition and are more likely to develop early neurological deterioration and in-hospital death than non-cancer patients with stroke.^{13, 14} In a case-control study, 32% of cancer patients with ischemic stroke had in-hospital death versus 13% of non-cancer patients with ischemic stroke.³⁷ Small retrospective studies have reported that high D-dimer levels may be predictive of early neurological deterioration and death in cancer-associated stroke.^{15, 38} However, the prognostic utility of D-dimer and other biomarkers in cancer-associated stroke requires confirmation in prospective studies with systematic assessments.

Cerebrovascular Pathophysiology

How Cancer Increases Stroke Risk

The exact reasons for increased stroke risk in cancer patients is uncertain and likely multifactorial (Figure 1). One probable contributor is acquired hypercoagulability from cancer itself. Supporting this hypothesis is the observation that the stroke risk associated with cancer is highest immediately after diagnosis, when cancer activity, and hence acquired hypercoagulability, is generally most intense and then attenuates over time as cancer activity decreases with treatment.¹⁰ Additionally, variable risks by cancer type and stage, which are

tumor-related factors directly linked to the presence and severity of cancer-mediated hypercoagulability, also implicates cancer's procoagulant effects as a driver of stroke risk in these patients.⁹

The mechanisms underlying cancer-mediated hypercoagulability are multifold. Tumors, particularly carcinomas, can release circulating microparticles into the bloodstream triggering thrombosis.³⁹ In the OASIS-Cancer study, investigators prospectively evaluated extracellular vesicles (i.e., microparticles) among 155 patients with active cancer and ischemic stroke and 158 controls with cancer only, stroke only, or healthy subjects.³⁹ They reported that cancer cell-derived extracellular vesicle levels correlated with D-dimer levels, a non-specific marker of hypercoagulability, and that cancer cell-derived extracellular vesicle levels were highest among the cancer and stroke group, particularly among patients with cryptogenic stroke. Furthermore, although cancer cells have been shown to express tissue factor, which can activate factor VIII and set off the coagulation cascade, the effects of these vesicles appeared to be mediated via tissue factor-independent mechanisms.¹⁹

Cancers also increase the levels of other procoagulant factors, including factor X, and they can release mucins that activate platelets and endothelial cells through binding of P- and L-selectins.¹⁹ Additionally, cancers stimulate neutrophils to release decondensed chromatin, leading to the formation of neutrophil extracellular traps (NETs), which promote inflammation and thrombosis.⁴⁰ Furthermore, cancers, particularly brain tumors, can overexpress podoplanin, a transmembrane sialoglycoprotein and a potent activator of platelet aggregation.⁴¹

Increased stroke risk in cancer patients could also be a consequence of anti-neoplastic treatments. Several retrospective studies have reported that platinum-based chemotherapy and angiogenesis inhibitors increase the risk of stroke and other thromboembolism.^{42–45} This may occur because chemotherapy releases microparticles from cancer cells, which enhance thrombin generation.⁴⁶ In addition, radiotherapy can cause vasculopathy through accelerated atherosclerosis or other mechanisms, which can then precipitate stroke.^{47–49} Radiation-induced vasculopathy is typically reported in the carotid arteries or its branches in patients with head and neck or brain cancers, but it can also affect the great vessels or aorta in patients with breast, lung, or lymphoma cancers who received chest wall radiation.^{48, 50, 51} Radiation involving the circle of Willis is more hazardous than cranial radiation elsewhere, and there is a dose-response relationship with higher radiation doses conferring increased stroke risk.^{47, 49} Most strokes from radiation vasculopathy develop many years after treatment.⁵²

A caveat is that increased stroke risk in cancer patients could be due to confounding bias from risk factors associated with both cancer and stroke, especially smoking. However, this is unlikely to fully explain the association between cancer and stroke because several cancers not tied to smoking, such as non-Hodgkin lymphoma, have been associated with increased stroke risk.^{9, 11, 53} In addition, the variable temporal pattern of stroke risk among cancer patients argues against confounding bias because differences in stroke risk factors between groups would be expected to produce uniform risk differences over time. Other factors that might contribute to the increased risk of stroke in cancer patients include

increased psychological stress, detection bias due to heightened surveillance, and underutilization and frequent interruption of antithrombotics because of bleeding concerns.¹⁹

Cancer-Related Stroke Subtypes

Stroke mechanisms are often unconventional or uncertain in cancer patients (Table 1).³² Compared to a 30% cryptogenic rate in the general population, about 50% of cancer-associated strokes are deemed cryptogenic after evaluation.^{30, 31} These cancer-related cryptogenic strokes tend to be associated with high D-dimer levels, infarctions in multiple vascular territories, and metastatic disease.^{32, 54, 55} One common theory is that many cryptogenic strokes in cancer patients are from cardioembolic manifestations of cancer-mediated hypercoagulability, specifically nonbacterial thrombotic endocarditis, which comprises sterile, platelet-fibrin vegetations on cardiac valves.³¹ Supporting this hypothesis is an older, highly-cited autopsy study of 256 cancer patients with cerebrovascular disease, which reported that nonbacterial thrombotic endocarditis was the leading cause of symptomatic ischemic stroke in this population.⁷ Furthermore, in a prospective study, among 74 patients with cancer and acute ischemic stroke, about half had microemboli detected on transcranial Doppler ultrasound, and presence of microemboli was associated with high D-dimer levels, suggesting an active central embolic source and hypercoagulable state in many of these patients.⁵⁶ However, nonbacterial thrombotic endocarditis is infrequently confirmed during life, even when transesophageal echocardiography is performed, consequently the exact stroke mechanism remains undetermined in many cancer patients.⁵⁷

Paradoxical embolism is another important consideration in cancer patients with cryptogenic stroke, as about 25% of the general population has right-to-left shunts and up to 20% of cancer patients develop venous thromboembolism.^{5, 58} In a study of 184 ischemic stroke patients, including 11 with comorbid cancer, right-to-left shunts were present in 55% of patients with cancer versus in 15% of those without.⁵⁸ Our group and others are conducting translational studies to better elucidate stroke mechanisms in cancer patients. In the ongoing Mechanisms Of ischemic STroke in Cancer patients (MOST-Cancer) prospective study (clinicaltrials.gov ID NCT02604667), we are comparing select hematological biomarkers, leukocyte RNA gene expression profiles, and transcranial Doppler microemboli detection rates between active cancer patients and matched stroke-only and cancer-only controls to evaluate the roles of hypercoagulability and cardioembolism in cancer-associated stroke.

Like in the general population, large artery atherosclerosis and small vessel disease are common stroke mechanisms in cancer patients, accounting for one-quarter to one-third of all events.^{31, 32} Besides shared risk factors such as smoking and obesity, cancer may promote atherosclerotic plaque formation and rupture through heightened systemic inflammation.⁵⁹ In addition, radiation, a common treatment for many cancers, promotes vasculopathy through accelerated atherosclerosis and injury to the vasa vasorum, thereby increasing long-term stroke risk.⁴⁸ Among 2201 survivors of Hodgkin lymphoma followed for a median of 18 years, radiation to the neck and mediastinum more than doubled the long-term risk of ischemic cerebrovascular disease.⁵¹ Pediatric brain tumor survivors are particularly

susceptible to the deleterious effects of radiation, and one study suggested that their incidence of cerebrovascular events is 100-fold higher than age-matched controls.⁴⁹

Less common but noteworthy stroke mechanisms in cancer patients include atrial fibrillation, septic embolism, intravascular coagulation, tumor embolism, intracranial vessel compression, hyperviscosity, and cerebral vein thrombosis. Recent data suggest that cancer may be associated with atrial fibrillation, a well-known stroke mechanism.⁶⁰ Besides shared risk factors, inflammation and oxidative stress may represent overlapping pathogenic pathways for cancer and atrial fibrillation.⁶⁰ Septic embolism should be considered in cancer-associated stroke because cancer patients are predisposed to infective endocarditis from frequent immunosuppression, indwelling catheters, and invasive procedures.⁷ Additionally, cancer patients can develop diffuse arterial thromboses from disseminated intravascular coagulation, including intracerebrally, causing stroke. This usually develops in patients with terminal cancer; however, leukemia sometimes presents in this fashion, and affected patients can be cured with emergent chemotherapy.⁶¹ Tumor embolism is another potential cause of stroke in cancer patients.³⁴ Responsible tumors generally involve the lung or heart, and access the arterial circulation by invading the pulmonary veins or cardiac chambers. Intracranial artery compression and invasion is another rare cause of stroke with cancer, typically occurring in patients with glioblastoma multiforme.⁵² Hyperviscosity occasionally causes stroke in patients with hematological malignancies. Besides arterial causes, cerebral vein thromboses should also be evaluated for in cancer patients with stroke. These events can occur because of hypercoagulability, complications of cancer treatments, or venous compression by contiguous tumor.⁷

Prognosis

Survival and Functional Outcomes

Among ischemic stroke patients, comorbid cancer is associated with increased stroke severity, early neurological deterioration, and in-hospital death.^{13, 37, 62} Median survival was 84 days in 263 patients with active solid or hematological cancer diagnosed with acute ischemic stroke at a quaternary-care cancer center.³¹ However, these patients may have been sicker than most cancer-stroke patients because of referral bias, and survival was considerably longer in patients whose stroke mechanism was identified. Predictors of mortality in cancer-associated stroke include stroke severity, metastases, diabetes, cryptogenic mechanisms, and elevated C-reactive protein and D-dimer levels.^{13, 38, 54} In addition, a single-center study reported that reducing D-dimer levels through chemotherapy and antithrombotics may be associated with prolonged survival.¹⁵ While promising, prospective multicenter studies with systematic outcome assessments are needed to confirm this hypothesis.

Despite high mortality, short-term functional outcomes are favorable in many cancer patients with stroke. According to one cohort study, active cancer patients' median Rankin score at hospital discharge for ischemic stroke was 3 (i.e., dependent but could walk without assistance) and 56% were discharged home.³¹ Another study reported that among cancer patients without early neurological deterioration after stroke, 51% had good 3-month functional outcomes (i.e., Rankin score 0–2).¹⁵

Recurrent Stroke Risk

Cancer patients with ischemic stroke face high rates of recurrence. In a retrospective study conducted at a cancer center, 31% of active cancer patients were diagnosed with a recurrent thromboembolic event by 3 months, including 13% with recurrent ischemic stroke, which is nearly threefold higher than typical recurrent stroke rates in non-cancer patients.^{31, 63}

Adenocarcinoma cancer histology independently predicted for recurrent thromboembolism.

³¹ Similarly, in a retrospective study conducted at a tertiary-care center in Korea, stroke recurrence occurred in 28% of cancer patients versus 13% of non-cancer patients, and unconventional stroke etiology was independently associated with stroke recurrence.¹⁴

Another study reported that high D-dimer levels are associated with early neurological deterioration and recurrent stroke.¹⁵ Besides adults with active cancer, childhood cancer survivors also face high rates of recurrent stroke, particularly in the long-term. Among 271 participants in the Childhood Cancer Survivor Study diagnosed with a first ischemic stroke during follow-up, 70 reported a second stroke at a median age of 32 years.⁶⁴ The 10-year cumulative incidence of late recurrent stroke was 21% in all patients, and 33% in those treated with 50 Gray of cranial radiation.⁶⁴ Therefore, there may be a U-shaped curve in terms of incident and recurrent stroke risk in cancer patients, whereby risk is highest soon after cancer diagnosis when hypercoagulability typically peaks due to heightened cancer activity and frequent chemotherapy, followed by a reduction in risk for years if cancer activity is controlled and remission or cure is achieved, followed again by a spike in stroke risk due to long-term effects of cancer treatments, particularly vasculopathy from radiation (Figure 2).

Treatments

Acute Recanalization Therapies

While cancer patients may be more likely to have contraindications to thrombolysis than non-cancer patients, active cancer by itself is not exclusionary for recanalization therapies.⁶⁵ Furthermore, although there have been no trials evaluating tissue plasminogen activator treatment in cancer patients with stroke, cohort studies have suggested that selective treatment in patients who otherwise meet eligibility criteria is likely safe. For example, among 18 patients with cancer (61% with metastases) and stroke treated with intravenous thrombolysis at a stroke center, 5.6% had symptomatic intracranial hemorrhage.⁶⁶ In a claims-based study of 32,576 patients with stroke treated with intravenous thrombolysis, 807 had comorbid cancer, and intracerebral hemorrhage rates were similar between patients with cancer (6.3%) and those without (6.4%).⁶⁷ In the United States, intravenous thrombolysis use in patients with acute stroke and comorbid cancer increased from 0.01% in 1998 to 4.23% in 2013 (unpublished data presented at ISC 2018). While steadily increasing, these utilization rates were consistently one-third less than rates in non-cancer patients with ischemic stroke.

There are few reports of intravenous thrombolysis in patients with primary or metastatic brain tumors.^{68, 69} While these case series report mostly low hemorrhage rates, publication bias is likely, and common sense dictates to avoid thrombolysis in patients with malignant brain tumors, as stroke mimics and risk of hemorrhage are likely high. However, intravenous

thrombolysis may be carefully considered in stroke patients with benign brain tumors, particularly if small and extraaxial.⁶⁵

Endovascular therapy is another treatment option for cancer patients with acute stroke but there are no trial data in this population. However, case series suggest that it might be beneficial for select patients with good premorbid functional status who develop large vessel occlusive strokes.⁷⁰ Furthermore, claims-based studies have reported that intracerebral hemorrhage rates after endovascular therapy are comparable between cancer and non-cancer patients.⁶⁷ Additionally, unlike intravenous thrombolysis, national rates of endovascular therapy utilization were similar between cancer (1.07%) and non-cancer patients (1.09%) with ischemic stroke in 2013 (unpublished data presented at ISC 2018); the reasons for this discrepancy are uncertain and require investigation.

Secondary Stroke Prevention

Owing to the lack of solid treatment data to guide clinicians, the optimal antithrombotic to prevent recurrent stroke in cancer patients is unclear. While many neurologists favor a personalized approach whereby the antithrombotic treatment strategy is dictated by patients' stroke mechanism, this practice can be challenging in cancer patients because roughly half their strokes are cryptogenic.³¹ Furthermore, even in cancer patients with known stroke mechanisms typically treated with antiplatelets, such as large artery atherosclerosis, cancer-mediated hypercoagulability may have contributed to or triggered their stroke, so it is possible that anticoagulation might benefit these patients. Conversely, while often suspected, hypercoagulable stroke mechanisms, such as nonbacterial thrombotic endocarditis, are rarely definitively diagnosed in cancer patients antemortem.⁵⁷ Therefore, substantial mechanistic dilemma exists in cancer-associated stroke, making a "precision medicine" approach difficult. Consequently, in clinical practice, many neurologists use theoretical considerations and institutional practice patterns to determine which antithrombotic agent(s) to prescribe (Table 2).

Anticoagulation has been recommended as first-line treatment for cancer-associated stroke, especially low-molecular weight heparin.²⁰ This approach represents an extrapolation from venous thromboembolism trials, which demonstrated that low-molecular weight heparins are superior to vitamin K antagonists for preventing recurrent thromboses in cancer patients.⁷¹ However, direct oral anticoagulants are an increasingly attractive option for these patients and the recently published Hokusai-VTE trial demonstrated that among 1050 randomized patients with cancer-associated venous thromboembolism, oral edoxaban (factor Xa inhibitor) was not inferior to subcutaneous dalteparin (low-molecular weight heparin) with respect to the composite outcome of recurrent venous thromboembolism or major bleeding.⁷² Interestingly, edoxaban led to less recurrent thromboembolism but more major bleeding than dalteparin. Other direct oral anticoagulants remain under investigation for cancer-associated thrombosis, including apixaban, which is being compared to dalteparin in the CARAVAGGIO, phase 3, randomized trial (clinicaltrials.gov ID NCT03045406). Nevertheless, besides a retrospective analysis of 7 patients with active cancer and cryptogenic stroke who were treated with a direct oral anticoagulant and had similar

outcomes compared to 41 similar patients treated with low-molecular weight heparin, there is limited data on the utility of direct oral anticoagulants for cancer-associated stroke.⁷³

In support of anticoagulation for cancer-related stroke are data from small retrospective studies demonstrating reductions in recurrent events, D-dimer levels, and transcranial Doppler microembolism with treatment.^{56, 74, 75} However, anticoagulation also has drawbacks, especially the increased risk of bleeding, which might outweigh any potential reductions in recurrent thromboembolism risk. This is particularly relevant for cancer patients, who already face up to a 20% annual major bleeding risk.⁷⁶ Additionally, recent data suggests that low-molecular weight heparin anticoagulation is associated with a threefold increased risk of intracerebral hemorrhage in patients with brain tumors.⁷⁷ Finally, anticoagulation is often expensive and burdensome, especially injectable heparins.

An alternative antithrombotic paradigm for cancer-associated stroke is antiplatelet therapy, which is the mainstay for most strokes, easy to administer, and generally safe. In addition, platelets play an important role in cancer growth and metastasis, so platelet inhibitors might have direct antineoplastic properties.⁷⁸ Aspirin, in particular, has been shown to reduce the risk of gastrointestinal cancer formation.⁷⁸ However, antiplatelet therapy may not sufficiently offset cancer-mediated hypercoagulability, which may play a role in many cancer-associated strokes.

There are limited data on the utility of different antithrombotic strategies for cancer-associated stroke. Jang and colleagues retrospectively analyzed 79 cancer patients with ischemic stroke treated with enoxaparin or warfarin in Korea.⁷⁹ During a mean follow-up of 4.9 months, 16% of warfarin-treated patients suffered recurrent stroke versus 3.4% of enoxaparin-treated patients; the incidence of major bleeding was similar between groups (10% with warfarin versus 6.9% with enoxaparin). Our group previously compared anticoagulation versus antiplatelet therapy among 172 patients with active cancer and ischemic stroke treated with some form of antithrombotic therapy.³¹ In this retrospective analysis, 52% were treated with therapeutic anticoagulation (mostly low-molecular weight heparin) and 48% were treated with antiplatelets (mostly aspirin). We found no difference between groups in rates of recurrent thromboembolism or death.³¹

We recently completed a pilot randomized trial comparing anticoagulation with enoxaparin to antiplatelet therapy with aspirin in patients with active cancer and acute ischemic stroke.⁸⁰ Patients with clear indications for anticoagulation (e.g., venous thromboembolism or atrial fibrillation) or antiplatelets (e.g., recent stent) were excluded. Among 49 eligible patients, 20 enrolled, equating to an enrollment rate of 41%. The top reason for enrollment failure was patient aversion to injections. Additionally, during follow-up, 60% of patients randomized to enoxaparin crossed over to aspirin because of discomfort with injections or cost of drug. These data suggest that a randomized trial of anticoagulation versus antiplatelet therapy in cancer patients with ischemic stroke is probably feasible, although an oral anticoagulant is preferred because it would likely improve recruitment and drug adherence. Given the considerations outlined above, we believe that such a trial is necessary to determine the optimal antithrombotic strategy for many cancer patients with ischemic stroke.

Conclusion

Stroke in cancer patients is more common than previously believed, and its frequency and impact will likely increase with continued improvements in cancer survival. Furthermore, new cancer diagnoses are associated with a substantially increased short- and long-term risk of incident and recurrent stroke, although the mechanisms underlying these heightened risks are uncertain, including the roles played by cancer treatments. Mirroring this mechanistic uncertainty is the lack of a clear optimal antithrombotic strategy to prevent stroke recurrence in these patients. Future research is needed to fill these knowledge gaps. This includes prospective studies to identify biomarkers that can reliably predict first and recurrent stroke in cancer patients, translational studies to elucidate the mechanisms of these strokes, and clinical trials to identify the best strategies to prevent and acutely treat cerebrovascular events in the cancer population.

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Figure 1.

Potential reasons for cancer patients' increased risk of ischemic stroke.

Diagram depicting the possible underlying explanations for cancer patients' heightened stroke risk. These include: (a) biological factors, such as cancer-mediated hypercoagulability, adverse effects of cancer treatments, and increased psychological stress after cancer diagnosis; (b) diagnosis-related factors, such as detection bias from heightened surveillance and underutilization or frequent interruption of antithrombotics because of bleeding concerns; and (c) shared risk factors, such as atrial fibrillation, obesity, and tobacco use. Most likely multiples factors are at play, some of which may be synergistic.

Figure 2.

Hypothesized line graph of cancer patients' suspected risk of ischemic stroke over time.

Based on the totality of current evidence, we hypothesize a U-point curve whereby risks are increased immediately before and in the year after cancer diagnosis when cancer-mediated hypercoagulability is generally at its peak, followed by a reduction or normalization in stroke risk for several years among those whose cancers are cured or put into long-term remission, followed again years later by progressively increasing risk due to the long-term effects of cancer treatments, particularly radiation vasculopathy.

Table 1

Common Causes of Ischemic Stroke in Patients with Cancer by ASCO Classification

Presumed Cause*	Usual Cancer Type	Cancer-Related Risk Factors
<i>Atherosclerosis</i>		
Intra- or extra-cranial large artery atherosclerosis	Smoking-related solid tumors or primary brain tumors	Prior radiation
<i>Small Vessel Disease</i>		
Cerebral small vessel disease	Solid, hematologic, or primary brain tumors	Prior radiation, VEGF inhibitors
<i>Cardioembolism</i>		
Atrial fibrillation	Solid or hematologic tumors	Bisphosphonate use
Cardiomyopathy	Breast cancer	Anthracycline and Trastuzumab chemotherapy
Infective endocarditis	Solid or hematologic tumors	Central venous catheter, leukopenia, sepsis, recent invasive procedures
Nonbacterial thrombotic endocarditis	Solid tumors, especially carcinomas, or lymphomas	Advanced cancer stage, refractory cancer, bone marrow transplantation
Paradoxical embolism	Solid, hematologic, or primary brain tumors	Venous thromboembolism, immobility, active chemotherapy
Tumor embolism	Primary or metastatic solid tumors of the lung or heart	Thoracic surgery
<i>Other</i>		
Cerebral intravascular coagulation	Solid or hematologic tumors	Refractory cancer, promyelocytic form of leukemia, sepsis
Cerebral vein thrombosis	Solid, hematologic, or primary brain tumors	L-asparaginase chemotherapy, tumors near venous sinuses
Hyperviscosity	Hematologic tumors	Hyperleukocytosis, thrombocytosis
Intracranial vessel compression	Glioblastoma	Tumor located near Sylvian fissure
Vasculitis	Solid or hematologic tumors	Fungal or varicella infection, intravascular variant of lymphoma

Abbreviations: VEGF, vascular endothelial growth factor.

* Causes are listed in alphabetic order according to ASCO stroke subtype classification.

Table 2**Pros and Cons of Anticoagulant or Antiplatelet Therapy for Cancer-Associated Ischemic Stroke**

<i>Anticoagulants</i>	
<i>Pros</i>	
Some studies suggest that they may reduce D-dimer levels, TCD microemboli, and short-term recurrent events in cancer patients with ischemic stroke	
More directly addresses cancer-mediated hypercoagulability, especially LMWHs, which have more “off-target” anticoagulant effects than direct oral anticoagulants	
LMWHs, in particular, may have some anti-neoplastic properties, explaining their superiority to vitamin K antagonists for treating cancer-associated venous thromboembolism	
<i>Cons</i>	
Higher bleeding risk than with antiplatelets, especially intracranially, which could outweigh any potential reductions in recurrent stroke risk	
Expensive, especially LMWHs and the direct oral anticoagulants	
LMWH forms are burdensome injectables that can be difficult to administer for cancer-stroke patients, hindering adherence	
<i>Antiplatelets</i>	
<i>Pros</i>	
Standard-of-care for most stroke patients; Level 1 evidence supporting their use	
Excellent safety profile	
May have direct anti-neoplastic properties through inhibition of tumor growth and spread	
Inexpensive	
Once daily oral administration	
<i>Cons</i>	
Less aggressive blood thinning, which might not sufficiently address cancer-mediated hypercoagulability and its contribution to stroke risk	
Aspirin, in particular, increases the risk of gastrointestinal ulcers and bleeding	

Abbreviations: TCD, transcranial Doppler; LMWH, low-molecular weight heparin.