REVIEW
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Ischemic Stroke and Cancer: Stroke Severely Impacts Cancer Patients, While Cancer Increases the Number of Strokes

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Background Cancer and ischemic stroke are two of the most common causes of death among the elderly, and associations between them have been reported. However, the main pathomechanisms of stroke in cancer patients are not well known, and can only be established based on accurate knowledge of the characteristics of cancer-related strokes. We review herein recent studies concerning the clinical, laboratory, and radiological features of patients with cancer-related stroke.

Main Contents This review covers the epidemiology, underlying mechanisms, and acute and preventive treatments for cancer-related stroke. First, the characteristics of stroke (clinical and radiological features) and systemic cancer (type and extent) in patients with cancer-specific stroke are discussed. Second, the role of laboratory tests in the early identification of patients with cancer-specific stroke is discussed. Specifically, serum D-dimer levels (as a marker of a hypercoagulable state) and embolic signals on transcranial Doppler (suggestive of embolic origin) may provide clues regarding changes in the levels of coagulopathy related to cancer and anticoagulation. Finally, strategies for stroke treatment in cancer patients are discussed, emphasizing the importance of preventive strategies (i.e., the use of anticoagulants) over acute revascularization therapy in cancer-related stroke.

Conclusion Recent studies have revealed that the characteristics of cancer-related stroke are distinct from those of conventional stroke. Our understanding of the characteristics of cancer-related stroke is essential to the correct management of these patients. The studies presented in this review highlight the importance of a personalized approach in treating stroke patients with cancer.
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Key Words cancer, stroke, ischemic, hypercoagulopathy, embolism, anticoagulants.

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Introduction

Systemic cancer and ischemic stroke are both common conditions, and are two of the most common causes of death among the elderly. The number of people living with cancer is increasing, and the steadily increasing proportion of elderly people in the world is predicted to result in an increase of approximately 50% in new cancer cases over the next 20 years, with the number of new cases each year rising from 10.9 million in 2002 to 16 million in 2020 (World Health Organization, Global action against cancer, 2005). In addition, improvements in treatment practice (cancer medicine) have the potential of improving survival by up to 15%. Therefore, the number of stroke patients with cancer is expected to rise with increases in the number of people living with cancer. Moreover, associations between cancer and stroke have been reported. Cerebrovascular disease occurs commonly in cancer patients, with 15% of cancer patients experiencing a thromboembolic event during their clinical

course.[1] As a consequence, the proportion of patients who have cancer is expected to increase among stroke patients.

The treatment of stroke in cancer patients can be challenging, requiring the development of specific treatment strategies. Although patients with systemic cancer usually have poor outcomes, their survival rate is increasing with the development of more effective cancer medicines. Early identification of stroke mechanisms may be important in cancer patients, because stroke mechanisms in cancer patients may differ from those in stroke patients without cancer. However, the mechanisms underlying stroke in patients with cancer are largely unknown.[2-4] The prevention and appropriate treatment of stroke in cancer patients require an accurate understand of its clinicoradiologic characteristics and pathogenic mechanisms.

Herein we review recent studies in which modern methods of stroke evaluation have been applied to identify the characteristics of stroke in cancer patients, such as biomarkers, multimodal magnetic resonance imaging (MRI), and embolism monitoring using transcranial Doppler ultrasound (TCD). This review covers the epidemiology, mechanisms, and acute and preventive treatments for cancer-related stroke.

Subtypes of Stroke and Cancer Differ between Patients with and without Conventional Stroke Mechanisms

The controversies regarding the characteristics of stroke in patients with cancer may be due to the involvement of both cancer-unrelated and cancer-related mechanisms in the development of stroke in cancer patients (Table 1). In cancer patients without conventional stroke mechanisms (CSM; e.g., atherosclerosis, cardioembolism, or lacunar), a cancer-specific mechanism can be considered as the main cause of stroke. We recently prospectively studied 161 patients registered from 6 centers in South Korea with active cancer who experienced acute ischemic stroke.[5] Stroke outside CSM occurred in a large proportion of cancer patients: CSM were absent in ~40% of stroke patients with cancer, and occurred with a higher frequency of cryptogenic mechanisms than in stroke patients without cancer (18%). Interestingly, tumor-specific mechanisms were unlikely to play a role in the development of stroke among patients exhibiting CSM, given that the distribution of stroke subtype among cancer patients with CSM was similar to that in stroke patients without cancer (Fig. 1).

The characteristics of cancer, including the type (primary cancer and pathologic type) and extent of cancer and the time interval from diagnosis of cancer and stroke, may be important in the development of stroke in patients with cancer. Patients with stroke had different primary cancers; lung cancer being the most common, followed by gastric and colorectal cancer (Table 2). When we compared this to the data from the Samsung Cancer Center, the proportion of primary cancer types did not differ between patients with and without stroke. The one exception was lung cancer, which was significantly more prevalent among stroke patients than among those without stroke. Among the pathologic type of lung cancer, adenocarcinoma was significantly more prevalent in patients without CSM than in those with CSM or those without stroke; about 70% of patients without CSM had adenocarcinoma, whereas about 70% of patients with cancer-un-

Table 1. Mechanisms underlying stroke in patients with cancer

Cancer-unrelated mechanisms
Conventional stroke mechanisms
Atherosclerosis, cardioembolic, lacunar, etc.
Cancer-related mechanisms
Coagulopathy by
Tumor cell (especially adenocarcinoma)-derived cytokines or microparticles
Tissue factor and cancer procoagulants
Cytokines such as tumor necrosis factor-α, interleukins
Intravascular coagulation or nonbacterial thrombotic endocarditis
Tumor occlusion
Tumor embolism (lung or cardiac), intravascular lymphoma
Direct tumor-related (metastasis or central nervous system tumor)
Vessel compression or infiltration
Treatment-related mechanisms
Chemotherapy causing coagulopathy, such as cisplatin, methotrexate, l-asparaginase, bevacizumab
Radiation or surgery causing vascular stenosis
Medical comorbidities, such as fungal infection or infective endocarditis

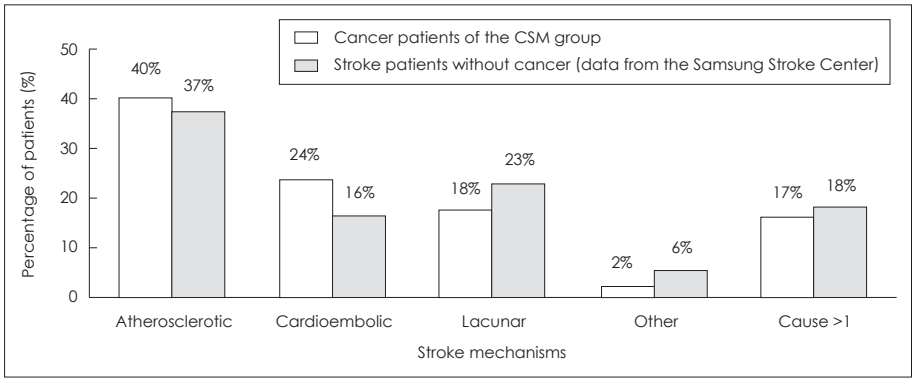


Fig. 1. Stroke subtypes in patients with vs. without cancer (data from the Samsung Stroke Center). Figure modified from Kim et al.[5] CSM: conventional stroke mechanisms.

Table 2. Cancer types in patients with vs. without stroke

Cancer type	Stroke patients with cancer, *n* (%)			Cancer patients without stroke, *n* (%)*
	Cryptogenic group	CSM group	Total	
Gastric	12 (18.8%)	13 (13.4%)	25 (15.5%)	1,764 (15.9%)
Colorectal	5 (7.8%)	18 (18.6%)	23 (14.3%)	1,229 (11%)
Breast	1 (1.6%)	1 (1.0%)	2 (1.2%)	999 (9%)
Hepatic	4 (6.3%)	9 (9.3%)	13 (8.1%)	1,274 (11.5%)
Lung	21 (32.8%)	26 (26.8%)	47 (29.2%)	1,276 (11.5%)†
Adenocarcinoma	15 (71.4%)†	6 (23.1%)	21 (44.7%)	421 (33.0%)
Cervical	0 (0%)	2 (2.1%)	2 (1.2%)	332 (3%)
Other	21 (32.8%)	28 (28.9%)	49 (30.4%)	4,228 (38.1%)
Total	64	97	161	11,097

*Data from the Samsung Cancer Center, †$p<0.001$, stroke patients with cancer vs. cancer patients without stroke.
CSM: conventional stroke mechanisms.

related stroke or those without stroke had nonadenocarcinoma types. Moreover, metastasis at the time of stroke was more prevalent among patients without CSM than among those with CSM.[5] These findings suggest that although occult tumor may cause coagulopathy and thromboembolism, patients with certain types of advanced-stage cancer are prone to cancer-related stroke.

Characteristics of Cancer-Related Stroke

The clinical and radiological features and laboratory findings may help to identify patients with cancer-related stroke mechanisms. There have been conflicting reports concerning whether or not risk factors in cancer patients (vs. noncancer patients) differ.[6-9] However, in previous studies, CSM were pooled with cancer-related mechanisms. In our study, patients with CSM were older and were more likely to have vascular risk factors than were patients without CSM.[5]

It has been reported that the pattern of the lesion identified on diffusion-weighted imaging (DWI) is correlated with the pathogenic mechanism underlying the stroke as well as the outcome after stroke.[10,11] The infarct pattern in cancer patients with stroke is seldom reported. DWI patterns of multiple lesions involving multiple arterial territories were more frequently observed in patients without CSM, whereas single/multiple lesions involving one arterial territory were observed more frequently in patients with CSM (Fig. 2).[5] Recent studies have demonstrated that concealed cancer should be considered in patients who exhibit multiple infarcts on DWI.[12]

Laboratory findings suggesting coagulopathy may also predict possible cancer-specific stroke mechanisms. The level of D-dimer, a plasmin-derived degradation product of cross-linked fibrin, is a direct measure of activated coagulation, and has been used in many previous studies as a measure of hypercoagulability.[4,13] Most patients without CSM had elevated D-dimer levels, and the levels were higher in patients with multiple embolic strokes than in patients with a single infarct or multiple infarcts within one vascular territory.[5] Our results and those of others suggest that there is a strong correlation between D-dimer level and the tumor burden and stage.[5,14-17]

Thus, the aforementioned parameters may predict possible cancer-related stroke mechanisms. Most patients with both DWI patterns of multiple lesions involving multiple arterial territories (pattern 3 or 4) and D-dimer levels of >1.11 μg/mL had can-

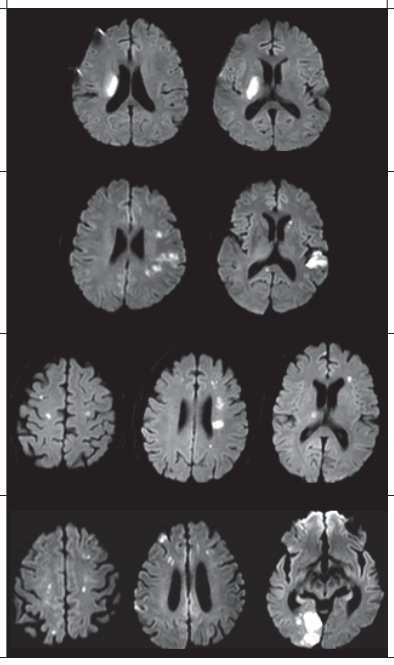
DWI lesion pattern	Examples		Conventional stroke mechanism	
		D-dimer	Present	Absent
Pattern 1 Single lesion		1.2±1.9	26 (27%)	5 (8%)
Pattern 2 Multiple lesions in a single arterial territory		2.8±5.6	51 (53%)	14 (22%)
Pattern 3 Multiple small lesions involving multiple arterial territories		11.7±14.3	11 (11%)	26 (41%)
Pattern 4 Multiple small and large disseminated lesions		10.3±20.0	9 (9%)	19 (30%)

Fig. 2. Diffusion-weighted imaging (DWI) lesion patterns in patients with and without conventional stroke mechanisms.

cer-specific stroke (31 of 36 patients, 86.1%), whereas CSM were found in most patients with none of these findings (36 of 40 patients, 90%). After adjusting for other factors, the DWI lesion pattern of multiple vascular territories and D-dimer levels of >1.11 μg/dL were independently associated with the possibility of cancer-related stroke mechanisms.[5] The area under the receiver operating characteristic curve for this stroke mechanism according to the presence of DWI pattern of multiple vascular territories or D-dimer levels of >1.11 μg/mL was 0.781 (95% confidence interval, 0.715-0.838).

Embolism Caused by Coagulopathy as the Main Mechanism of Stroke

A recent study that monitored embolic signals using TCD showed that embolisms caused by coagulopathy could be the main pathomechanism underlying cancer-related stroke.[14] A routine TCD study to detect embolism cannot generally be recommended for routine diagnostics in stroke patients due to its low sensitivity; in one study, embolic signals were detected in only 5.7% of unselected stroke patients.[18] However, the frequency of embolic signals on TCD suggestive of embolic origin is very high in cancer patients with acute ischemic stroke.[14] An embolic signal was observed in almost 50% of cancer patients with acute ischemic stroke, but more frequently in patients without CSM (58%) than in those with CSM (33%)(Fig. 3A). Moreover, the number of embolic signals was correlated with the D-dimer levels in patients without CSM but not in those with CSM (Fig. 3C and D), and the use of anticoagulation dramatically decreased the D-dimer levels (supplementary Fig. 1).[14] The detection of an embolic signal by TCD may provide clues regarding the cancer-specific mechanism related to hypercoagulopathy, and may be used to monitor the effect of treatment in the acute stroke period.

The source of the embolism causing multiple embolic strokes in cancer patients is unknown. Nonbacterial thrombotic endocarditis (NBTE) involves the deposition of small sterile vegetations on the heart valve leaflets and is most commonly found in patients with cancer. DWI has revealed NBTE patterns, with all patients with NBTE exhibiting multiple widely distributed large and small strokes (pattern 4).[19] In our data, more than 40% of patients without CSM showed disseminated small lesions (pattern 3) on DWI, and transesophageal echocardiography did not usually reveal vegetations. These findings suggest that intravascular clot formation is one of the main sources of such embolisms.

Thrombosis as a complication of cancer was first proposed by Trousseau in 1865, but the precise mechanisms underlying coagulopathy in cancer patients remain to be established. It has been suggested that substances in tumor cells, such as cysteine proteases, tissue factor, and sialic acid moieties of mucin, exhibit procoagulant activity, resulting in the activation of factors X and VII.[2,20] In addition, aggressive antitumor therapy may also increase the risk of thrombosis.[21]

Membrane-derived microvesicles are reported to be functional in that they support the tumor environment, such as neovas-

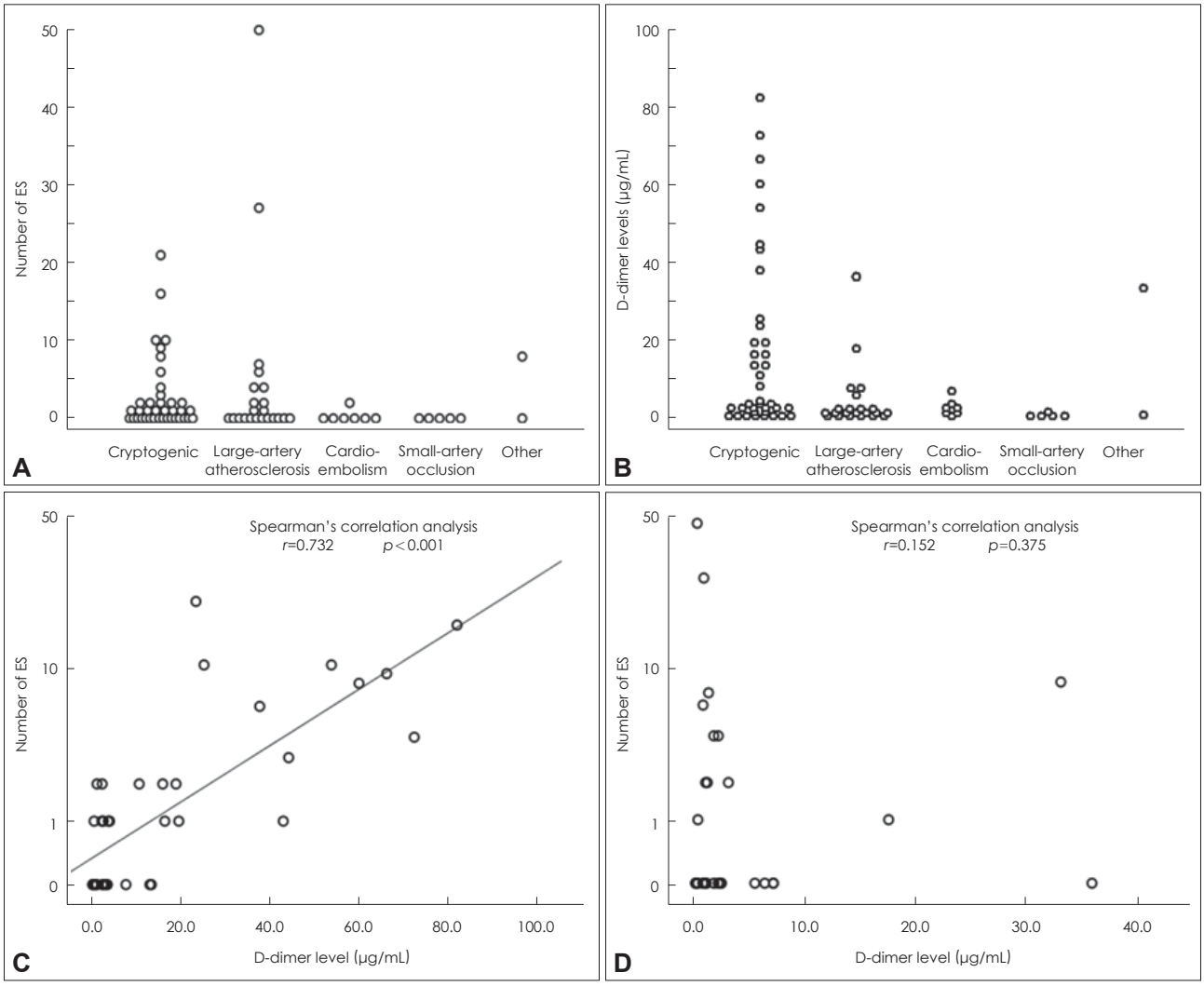


Fig. 3. Numbers of embolic signals (ES) on transcranial Doppler ultrasound (A) and D-dimer levels (B) for each stroke subtype. The scatterplot shows the correlation between the number of ES and D-dimer levels by subtype of ischemic stroke. (C) Patients without conventional stroke mechanisms (CSM) and (D) those with CSM. Figure modified from Seok et al.[14]

cularization in cancer patients.[22,23] Tissue-factor-bearing microvesicles were associated with the activation of coagulation in patients with colorectal cancer.[24-26] The levels of tissue-factor-positive microvesicles were elevated in cancer patients and were correlated with D-dimer levels, suggesting that tissue-factor-bearing microvesicles are involved in the activation of coagulation in cancer patients.[25] Tissue factor is not only the primary cellular initiator of blood coagulation, it is also a modulator of angiogenesis and metastasis in cancer.[24] Further studies are needed on preventive strategies targeting tissue factors to prevent coagulopathy and to control the tumor environment.

Acute and Preventive Treatment Strategies for Cancer-Related Stroke

Stroke patients with CSM should be treated according to the stroke subtype (e.g., atherosclerotic or lacunar), because the mechanisms underlying the stroke in these patients are unlikely to differ from those of stroke patients without cancer.[5] However, the optimal acute treatment and preventive strategies for cancer-related stroke remain to be established.

In the setting of acute ischemic stroke, recanalization therapy remains the principal therapeutic approach. The use of thrombolytics within the therapeutic time window is not contraindicated in cancer patients under the current guidelines for acute stroke therapy. However, the response to thrombolysis may differ between stroke patients with and without cancer. Multimodal MRI, including DWI and perfusion-weighted imaging, may help in the selection of patients for recanalization therapy.[27] Patients who exhibited a target mismatch pattern (substantial penumbra and small core) had a favorable clinical response to recanalization therapy.[28] However, the target mismatch profile is seldom

observed in cancer-related stroke. Patients with cancer-related stroke often exhibit normal perfusion-weighted imaging and angiographic findings, even in the presence of multiple infarcts and severe neurological deficits. Patients with higher D-dimer levels are less likely to exhibit the target mismatch pattern (unpublished data). Moreover, patients with cancer-related stroke often present with progressive neurological deficits over hours to days (or even weeks) rather than sudden catastrophic events with initial maximum deficits at onset (a representative case is shown in supplementary Fig. 2). In many patients, multifocal thromboembolism culminates in widespread infarcts of various sizes, producing confusion, lethargy, or dementia.[19] Thus, it is conceivable that patients with cancer-related stroke will often be ineligible for thrombolysis (outside the therapeutic time window) or unlikely to have a favorable response to thrombolysis (absence of penumbrae) at the time of presentation of ischemic symptoms.

In contrast, preventing recurrent embolism is important in cancer-related stroke. Considering the characteristics of the presenting symptoms (i.e., encephalopathy), the ischemic zone assessed by MRI (i.e., relative lack of ischemic penumbrae), and a higher rate of recurrent embolism in cancer-related stroke patients, strategies for stroke treatment in cancer patients should focus on correction of the coagulopathy using appropriate anticoagulants, rather than the resolution of a target mismatch profile.

Standard strategies for anticoagulants to prevent recurrent embolism are not yet established.[29] Intravenous (or subcutaneous) unfractionated heparin is the preferred treatment, but life-long maintenance on unfractionated heparin is not practical and may result in serious problems, especially hemorrhagic complications. Oral vitamin K antagonists (such as warfarin) and low-molecular-weight heparin could be appropriate alternatives. Several studies have successfully substituted low-molecular-weight heparin for unfractionated heparin in managing Trousseau's syndrome. Thromboprophylaxis using heparin or low-molecular-weight heparin is currently recommended in cancer patients as a prophylactic to prevent venous thromboembolism (deep venous thrombosis or pulmonary embolism).[30,31] There have been two large clinical trials of the use of low-molecular-weight heparin to prevent thrombosis in patients with cancer.[32,33] In patients with venous thromboembolism, low-molecular-weight heparin was more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without the risk of bleeding.[32] In patients with metastatic or locally advanced cancer who were receiving chemotherapy, the prophylactic use of low-molecular-weight heparin reduced the incidence of thromboembolic events.[33] In addition, a risk model predictive of chemotherapy-associated venous thromboembolism has been validated based on laboratory findings and the characteristics of cancer.[30] However, nether direct evidence nor guidelines are available in stroke patients with cancer. Further studies are therefore needed in the field of stroke.

Conclusion

The studies presented in this review highlight the importance of a personalized approach in treating stroke patients with cancer. The current knowledge can be summarized as follows:

1) Cancer is a prothrombotic condition that often manifests as a stroke.

2) Stroke with a cancer-specific mechanism occurs in a large proportion of cancer patients. With the increase in the number of people living with cancer, this type of stroke could become one of the prevalent stroke subtypes in the future.

3) The characteristics of cancer-related stroke are very distinct from those of conventional stroke. Embolism caused by cancer-related coagulopathy is the main mechanism underlying cancer-related stroke.

4) Improving our understanding of the characteristics of stroke in cancer patients using modern diagnostic evaluations is essential to the correct management of these patients.

Conflicts of Interest

The authors have no financial conflicts of interest.

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