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Review Article

Cancer-Associated Stroke and Acute Endovascular Reperfusion Therapy

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Since stroke is often associated with cancer, acute stroke patients with cancer undergoing endovascular therapy (EVT) are not uncommon. Reportedly, the proportion of such cases is approximately 6%–7% of all stroke EVT cases. Ischemic stroke in patients with active cancer (cancer-associated stroke) includes not only strokes caused by cancer-related hypercoagulability but also coincident strokes due to common etiologies, strokes associated with tumor emboli, direct tumor invasion of blood vessels, and strokes associated with cancer therapy. Stroke caused by cancer-related hypercoagulability itself encompasses various entities, including paradoxical embolism, stroke due to nonbacterial thrombotic endocarditis, and in situ arterial occlusion due to disseminated intravascular coagulation or thrombotic microangiopathy. Thus, diverse mechanisms contribute to cancer-associated stroke, emphasizing the need to consider individualized treatment strategies for acute cases involving large vessel occlusion. Observational studies have shown that EVT for cancer-associated stroke results in poorer clinical outcomes, but with comparable rates of successful reperfusion and symptomatic intracranial hemorrhage when compared with stroke patients without cancer. This suggests that denying patients EVT solely on the basis of comorbid active cancer is inappropriate, and decision-making should be shared with the patients and their families, preferably through a multidisciplinary team approach. Thrombi retrieved from patients with stroke caused by cancer-related hypercoagulability have unique characteristics, being predominantly platelet rich and difficult to retrieve. Preprocedural imaging and serum biomarkers, including the hyperdense vessel sign on non-contrast CT, susceptibility vessel sign on T2* or susceptibility-weighted MRI, three-territory sign on MRI, and D-dimer levels, are valuable in evaluating the stroke subtype and thrombus features. Thrombectomy techniques, such as contact aspiration and stent retriever monotherapy, have shown varying degrees of effectiveness for stroke caused by cancer-related hypercoagulability, warranting further study. After reperfusion therapy, appropriate treatment for the prevention of stroke recurrence should be initiated, considering the specific stroke subtypes. In conclusion, cancer-associated stroke encompasses diverse subtypes, and thrombi associated with stroke caused by cancer-related hypercoagulability present various challenges for thrombectomy. Individualized treatment approaches based on underlying mechanisms are essential for improving outcomes in acute stroke patients with active cancer. Optimization of preprocedural diagnosis, EVT techniques, and secondary prevention of stroke caused by cancer-related hypercoagulability will lead to better management of these patients and enhance their quality of life.

Keywords cancer, stroke, cancer-associated stroke, endovascular therapy, nonbacterial thrombotic endocarditis

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Introduction

Since the efficacy of endovascular therapy (EVT) for acute stroke due to large vessel occlusion was clearly proved by five pivotal trials in 2015,[1–5] EVT has become the standard of care and is widely performed. Since it is well known that the coexistence of cancer and stroke is often observed, acute stroke patients with cancer undergoing EVT are not uncommon, as seen by the fact that approximately 6%–7% of all stroke EVT cases reportedly have cancer.[6–8]

This review outlines the mechanisms of ischemic stroke in patients with cancer (in this review, ischemic stroke

occurring in patients with active cancer are referred to as cancer-associated stroke); the efficacy of EVT; treatment strategies, including preprocedural evaluation; and prevention of recurrence after reperfusion therapy.

Mechanism of Cancer-Associated Stroke

Cancer-related hypercoagulability, particularly induced by active (advanced/metastatic) cancer, can cause thromboembolic events and is known as Trousseau's syndrome.[9] Recently, the term cancer-associated thrombosis has been used to encompass all arterial and venous thrombotic events occurring in cancer patients.[10] Ischemic stroke occurring in patients with cancer includes not only strokes caused by cancer-related hypercoagulability but also coincident strokes of common etiologies (such as atherothrombotic, cardioembolic, and lacunar stroke), strokes associated with tumor emboli, direct tumor invasion of blood vessels, and strokes related to cancer therapy (chemotherapy, radiotherapy, and others).[11,12] Cases of stroke caused by a pulmonary vein stump thrombus after lobectomy for lung cancer have often been reported in recent years.[13,14] Stroke caused by cancer-related hypercoagulability also encompasses various other entities, including (certain types of) paradoxical embolism, stroke due to nonbacterial thrombotic endocarditis (NBTE), or in situ arterial occlusion due to disseminated intravascular coagulation or thrombotic microangiopathy.[11,12] Moreover, cancer-related cryptogenic stroke, defined as a cryptogenic stroke occurring in patients with active cancer, with coagulation abnormalities (elevated D-dimer levels, etc.) and/or with multiple lesions in multiple vascular territories is also regarded as a stroke caused by cancer-related hypercoagulability.[12,15] Therefore, since there are diverse mechanisms of cancer-associated stroke, it is necessary to take into account the underlying mechanism in each case when considering the treatment strategy for acute cancer-associated stroke.

Effectiveness of EVT for Cancer-Associated Stroke

Table 1 presents the results of observational studies on EVT for acute stroke, including some cases with intravenous thrombolysis alone, for cancer-associated stroke.[16–27] Although previous studies have often reported poor functional and vital outcomes in patients with cancer-associated stroke, they did not demonstrate a significant decrease in the rate of successful reperfusion or a significant increase in symptomatic intracranial hemorrhage (ICH) after the thrombectomy procedure compared with that in cancer-free stroke patients. In the SECRET study by Yoo et al.,[20] no significant intergroup difference was found in the change in National Institutes of Health Stroke Scale score 24 hours after treatment (median change in score of 2.5 in the active cancer group vs 3 in both no cancer and non-active cancer groups, $p = 0.844$), and approximately half of the patients with active cancer (45.5%) achieved a modified Rankin Scale score of ≤ 3 at 3 months. Two recent studies analyzing large population-level patient databases showed that there was no significant difference in the odds of discharge to home and ICH after EVT between acute stroke patients with metastatic cancer and those without cancer (except for in-hospital death).[6,28] It is, therefore, evident that excluding patients as EVT candidates based solely on the presence of comorbid active cancer is inappropriate. From **Table 1**, it can be observed that patients with cancer-related cryptogenic stroke have particularly poor outcomes among patients with cancer-associated stroke.[18,20,26,27] When patients under best supportive care (BSC) and with a short life-expectancy develop acute stroke, making a decision about the eligibility for EVT might be difficult. However, some reports have shown that EVT helps such patients to maintain their quality of life (QOL).[29,30] Hence, decision-making should be a shared process with the patients and their families, preferably through a multidisciplinary team approach, based on the expected efficacy/risks of EVT and goals of BSC (symptom relief, maintenance of QOL, etc.).[30]

Treatment Strategy for EVT in Stroke Caused by Cancer-Related Hypercoagulability

In a histological analysis of retrieved thrombi from acute stroke patients with active cancer, Park et al.[31] demonstrated that confirmed NBTE cases exhibited platelet-rich, erythrocyte-poor thrombi, which align well with the reported composition of NBTE thrombi in extracted heart valves. They also revealed that cancer-related cryptogenic stroke cases have a similar thrombus composition as NBTE. Furthermore, cases with active cancer whose stroke is confirmed as being one of the common subtypes exhibited a similar thrombus composition as those with inactive cancer or without cancer. This strongly suggests that cancer-related cryptogenic stroke and NBTE have almost identical pathomechanisms related to cancer-related hypercoagulability, and cancer-related cryptogenic stroke may encompass strokes due to undiagnosed NBTE in cases of

Table 1 Summary of observational studies on EVT for cancer-associated stroke

Author (year)	Disease subtype	N	Age, years, mean ± SD or median (IQR)	Baseline NIHSS score, mean ± SD or median (IQR)	P-value	Successful reperfusion, %	P-value	Symptomatic ICH, %	P-value	mRS score 0–2 at 3 months, %	P-value	Mortality at 3 months, %	P-value
Stroke with active cancer (cancer-associated stroke) versus control													
Lee et al. (2019)[16]	With active cancer	26	63.2 ± 11.6	14 (10–18)	0.517	88.5	0.723	57.7*	0.034	23.1	2.34 (1.05–5.25)†	30.8	0.003
	No cancer	227	68.8 ± 11.3	13 (9–17)		90.7		38.7*		41.9		8.8	
Sallustio et al. (2019)[17]**	With active cancer	24	69 ± 10.1	14.2 ± 5.2	0.97	76.9	0.67	0	1	41.6	0.14	29.1	0.28
	No cancer	24	70.7 ± 9.3	14.1 ± 4.9		61.5		0		66.6		12.5	
Cho et al. (2020)[18]	With active cancer	27	69.04 ± 9.95	11 (7–14)	0.36	85.2	0.8	11.1	0.6	37	0.84	33.3	<0.001
	Without active cancer	351	70.12 ± 11.46	12 (9–15)		82.6		16.2		39.6		8.2	
Ozaki et al. (2021)[19]	With active cancer	18	68.5 ± 26.3	16.5 ± 6.5	ND	94.7	0.13	0	0.2593	22.2	0.0331	16.7	0.9622
	Without active cancer	282	71.4 ± 15.3	15.8 ± 7.8		80.9		6.3		48.2		17.1	
Yoo et al. (2021)[20]**	With active cancer	62	68.2 ± 12.6	14 (11–19)	0.002	80.5	0.289	0	0.867	36.4	0.002	41.8	3.973 (2.528–6.245)‡
	With non-active cancer	78	73.1 ± 10.3	11 (5–16)		71.1		1.3		60.8		14.9	
	No cancer	1198	68.1 ± 11.8	12 (7–17)		80.9		1.9		60.7		8.8	
Ciolli et al. (2021)[21]	With active cancer	14	73 (61–78)	20 (10–23)	0.29	71	0.52	1.5	0.22	21	0.16	6.4	<0.01
	No cancer	267	72 (60–79)	16 (10–21)		78		6		44		1.4	
Joshi et al. (2022)[22]	With active cancer	19	70.9 ± 11.6	22 ± 7.5	NS	89.5	0.88	57.89*	<0.001	46.5	0.54	40	NS
	Without active cancer	95	70.7 ± 11.4	22 ± 9.5		91.5		6.49*		45.2		22.1	
Verschoof et al. (2022)[23]	With active cancer	124	69 ± 11	16 (12–19)	0.275	67.8	1.40 (0.95–2.07)§	6.5	1.12 (0.53–2.34)§	22.6	0.50 (0.31–0.81)§	52.2	3.17 (2.07–4.85)§
	No cancer	2459	70 ± 14	16 (11–19)		60.5		5.9		42.1		26.5	
Mattingly et al. (2022)[24]	With active cancer	25	70.6 ± 13.3	14.1 ± 5.8	0.301	88	0.436	28*	0.795	36	0.359	40	0.018
	Without active cancer	259	71.3 ± 14.0	15.6 ± 6.7		84		31*		46		20	

Table 1 (Continued)

Author (year)	Disease subtype	N	Age, years, mean ± SD or median (IQR)	Baseline NIHSS score, mean ± SD or median (IQR)	P-value	Successful reperfusion, %	P-value	Symptomatic ICH, %	P-value	mRS score 0–2 at 3 months, %	P-value	Mortality at 3 months, %	P-value
Federica et al. (2023)[25]	With comorbid cancer	152	76.4 (66.7–81.8)	17 (12–20)	NS	72.8	0.742	6.8	0.324	38.9	0.911	35.4	0.012
	No cancer	152	76.3 (66.7–81.2)	17 (12–20)		71.2		4.2		38.3		22.1	
	With metastatic cancer	42	ND	ND	ND	ND	ND	ND	ND	38	0.846	48	0.018
	With non-metastatic cancer	60	ND	ND		ND		ND		40		25	
Cancer-related cryptogenic stroke versus stroke due to other etiologies in patients without cancer													
Jung et al. (2018)[26]	Cancer-related cryptogenic stroke	19	69 (58–75)	16 (6–20)	0.004	63	0.238 (0.082–0.692)¶	ND	ND	16	0.008	63	<0.001
	Large artery atherosclerosis	105	69 (64–76)	12 (7–17)		84		ND		54		4	
	Cardiogenic embolic stroke	205	73 (65–79)	15 (10–20)		84		ND		44		13	
Lee et al. (2021)[27]	Cancer-related cryptogenic stroke	34	64.5 ± 11.4	18 (11–23)	0.29	76.5	0.103	41.2*	0.037	4‖	0.026	26.5	<0.001
	Stroke due to other etiologies	307	68.9 ± 14.0	15 (8–19)		87.6		23.8*		3‖		6.8	
Cancer-related cryptogenic stroke versus stroke due to other etiologies in patients with active cancer													
Cho et al. (2020)[18]	Cancer-related cryptogenic stroke	13	ND	ND	ND	84.6	ND	7.7	ND	21.4	ND	42.9	ND
	Stroke due to other etiologies	14	ND	ND		85.7		14.3		53.8		23.1	
Yoo et al. (2021)[20]**	Cancer-related cryptogenic stroke	22	62.6 ± 13.4	14.5 (9–22)	0.663	71.4	0.411	0	NS	9.5	0.003	85.7	<0.001
	Stroke due to other etiologies	40	71.3 ± 11.2	14 (12–17)		85.2		0		52.9		24.3	

⋆: Any ICH.
†: aOR (95% CI) of the active cancer group for a shift toward poor outcomes.
‡: Hazard ratio (95% CI) of the active cancer group for 6-month mortality compared with the no cancer group.
§: aOR (95% CI) of the active cancer group.
¶: aOR (95% CI) of the cancer-related cryptogenic stroke group compared with the cardiogenic embolic stroke group.
‖: Median value of mRS score at 3 months.
⋆⋆: Studies of Sallustio et al. and Yoo et al. included patients who received intravenous thrombolysis alone.
aOR: adjusted odds ratio; CI: confience interval; ICH: intracranial hemorrhage; IQR: interquartile range; mRS: modified Rankin Scale; ND: not described; NIHSS: National Institutes of Health Stroke Scale; NS: not significant; SD: standard deviation

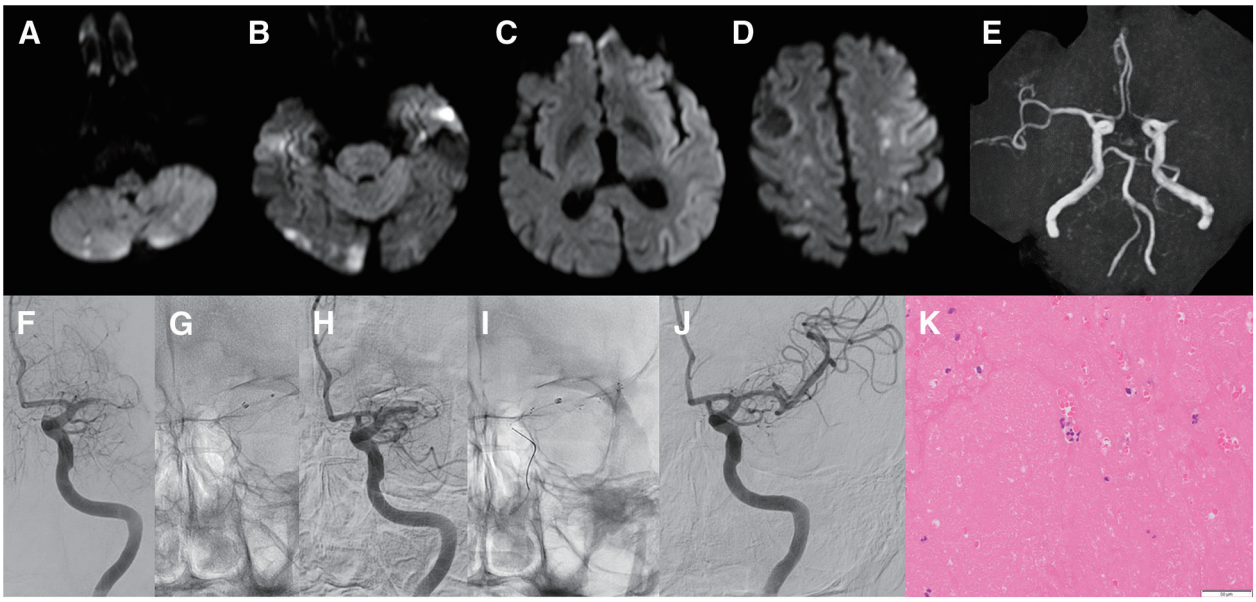

Fig. 1 A 63-year-old man with advanced lung cancer underwent endovascular thrombectomy for occlusion of the left MCA M1 segment. (**A**–**D**) Diffusion-weighted MR images at symptom onset showed multiple scattered ischemic lesions in multiple (anterior and posterior, bilateral) arterial territories (three-territory sign), in addition to an extended infarction in the left MCA-M1 territory. (**E**) MRA at symptom onset showed occlusion of the left MCA-M1 segment. (**F**–**J**) Endovascular treatment. Abrupt occlusion of the proximal M1 segment of the left MCA was detected (**F**). We first attempted to recanalize the occluded vessel by contact aspiration using a Penumbra ACE60 aspiration catheter (Penumbra Inc., Alameda, CA, USA) (**G**), although no recanalization was obtained (**H**). Next, we applied a technique combining the Penumbra aspiration catheter with a Solitaire Platinum revascularization device (Medtronic, Minneapolis, MN, USA) 6 mm in diameter and 40 mm in length (**I**). Complete reperfusion was achieved by the combined procedure (**J**). (**K**) Hematoxylin and eosin staining of the retrieved clot magnified 400× showed thrombus almost completely occupied with fibrin/platelet components (by courtesy of Dr. Sakamoto N, Department of Pathology and Neurosurgery, Institute of Medicine, University of Tsukuba). MCA: middle cerebral artery

insufficient workup. Based on examinations using hematoxylin–eosin staining (which cannot differentiate between platelets and fibrin), both Fu et al.[32] and Kataoka et al.[33] reported that stroke patients with active cancer have a higher proportion of fibrin/platelet-rich thrombi. In addition, Fu et al.[32] showed that retrieved thrombi from adenocarcinoma cases (adenocarcinomas, especially mucin-producing ones, often serve as the underlying disease for NBTE) exhibit a higher proportion of platelets compared to those from non-adenocarcinoma cases. Erythrocyte-rich thrombi have been shown to have a higher reperfusion rate after stent retriever thrombectomy,[34,35] particularly due to their high viscosity and deformability and low elasticity and hardness.[36] Conversely, frictional resistance and hardness are known to increase with an increase in the fibrin content and proportion of fibrin/platelets (especially platelets), respectively,[37,38] indicating that the effectiveness of stent retrievers might be limited in non-erythrocyte-rich thrombi. Indeed, Jung et al.[26] reported a lower reperfusion rate in patients with cancer-related cryptogenic stroke compared to that in those with other subtypes (adjusted odds ratio [aOR], 0.238; 95% confidence interval [CI], 0.082–0.692). Lee et al.[27] and Yoo et al.[20] also showed numerically lower reperfusion rates in cancer-related cryptogenic stroke cases.

Jeon et al.[39] demonstrated that contact aspiration, including the combined use of stent retrievers, demonstrated superior reperfusion efficacy compared to stent retriever monotherapy in patients with cancer-related cryptogenic stroke. This was attributed to mechanisms such as a reduction in frictional resistance by drawing the proximal part of the thrombus into the aspiration catheter, thereby decreasing the contact area of the thrombus with the vessel. On the other hand, Ozaki et al.[19] reported that contact aspiration monotherapy resulted in a lower reperfusion rate compared to stent retriever monotherapy or their combined use in acute stroke patients with active cancer. This could be because Ozaki et al.'s study might have included patients with coincident stroke with a common etiology (other than stroke caused by cancer-related hypercoagulability), which could be one of the factors contributing to the inconsistency of the results between studies. Further study is needed regarding the comparative efficacy of thrombectomy techniques for stroke caused by cancer-related hypercoagulability. In our institution, for cases suspected to be with stroke caused by hypercoagulability, we first performed contact aspiration thrombectomy, considering the potential need for transitioning to a technique requiring the combined use of a stent retriever (**Fig. 1**).

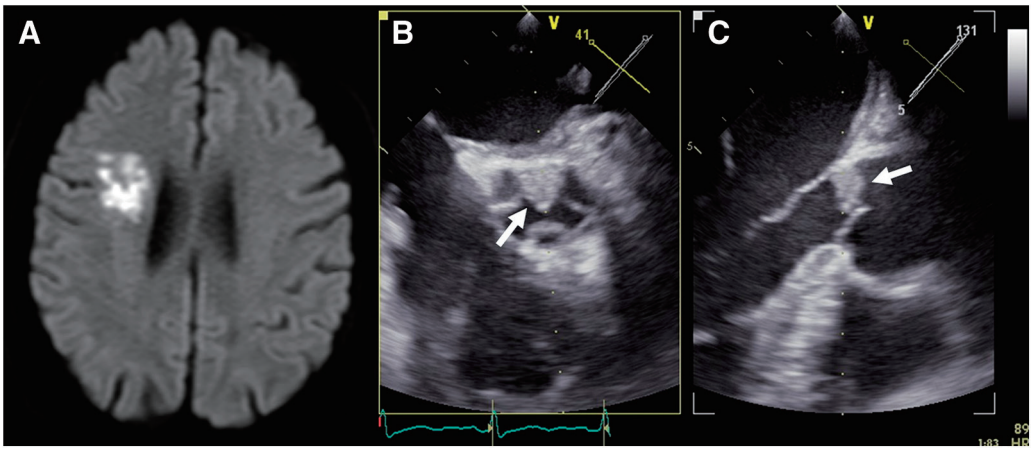

Fig. 2 A 70-year-old woman with advanced uterine cancer developed acute ischemic stroke due to NBTE during oral anticoagulant therapy using edoxaban for pulmonary embolism/deep venous thrombosis. Subcutaneous UFH was started, with no subsequent ischemic stroke over a 19-month period after stroke onset. (**A**) Diffusion-weighted MR images at symptom onset showed an acute ischemic lesion in the white matter of the right frontal lobe. (**B** and **C**) Transesophageal echocardiography short (**B**) and long (**C**) axis views revealed vegetations on the aortic valve (white arrow). NBTE: nonbacterial thrombotic endocarditis, UFH: unfractionated heparin

Imaging and Serum Biomarkers for Preoperative Diagnosis of Stroke Caused by Cancer-Related Hypercoagulability

Both the hyperdense vessel sign (HVS) on non-contrast head CT and the susceptibility vessel sign (SVS) on MRI T2*- or susceptibility-weighted images indicate erythrocyte-rich thrombi.[40–42] As mentioned earlier, retrieved thrombi from cases with stroke caused by cancer-related hypercoagulability exhibit minimal erythrocyte components, as evidenced by Jung et al.'s study,[26] where all 19 cases of cancer-related cryptogenic stroke showed absence of SVS. Beyeler et al.[43] also showed a significant association between absence of SVS and active cancer (aOR, 3.14; 95% CI, 1.45–6.80) from a large thrombectomy cohort analysis including a total of 2256 cases. Additionally, platelet-rich thrombi have been reported to show isoattenuation (Hounsfield Unit value <50) on non-contrast CT.[44] The absence of HVS/SVS findings might, thus, suggest the presence of stroke caused by cancer-related hypercoagulability in patients with cancer-associated stroke. The presence of the three-territory sign on MR diffusion-weighted imaging (multiple acute ischemic lesions in both the anterior and posterior circulation territories, as shown in **Fig. 1A**–**1D**) is reported to be closely associated with cancer-related cryptogenic stroke or stroke caused by cancer-related hypercoagulability,[45,46] and could be helpful in the diagnostic process. Furthermore, elevated D-dimer and tumor marker levels (especially CA125 and CA19-9, which are believed to directly activate prothrombin through their sialic acid residues in the blood, and potentially induce NBTE and intravascular thrombus formation)[47] should be considered as reference findings for assessing the stroke mechanism and thrombus features.

Prevention of Stroke Recurrence after Reperfusion Therapy

Appropriate treatment against stroke recurrence is necessary after reperfusion therapy. A comprehensive workup of the stroke etiology and embolic sources (including transthoracic/-esophageal echocardiography, right-to-left shunt evaluation, continuous cardiac monitoring, etc.) should be conducted, and antithrombotic therapy tailored to the specific etiology should be initiated.

Among direct oral anticoagulants (DOACs), anti-Xa agents have shown efficacy in the management of deep vein thrombosis associated with cancer,[48] and might have potential in the secondary prevention of paradoxical embolism in patients with active cancer. However, warfarin is known to be ineffective in the prevention of recurrence of stroke caused by cancer-related hypercoagulability, especially of NBTE, and the effectiveness of DOACs for this purpose also remains unclear (**Fig. 2**). Heparin (low-molecular weight heparin and unfractionated heparin [UFH]) has been suggested to have preventive effects on recurrent stroke caused by cancer-related hypercoagulability by acting on various pathways involved in thrombus formation (e.g., inhibiting the interaction between mucin and selectin by blocking its

binding to selectin ligands).[9] Yamaura et al.[49] reported in a study on cancer-related cryptogenic stroke complicated by deep vein thrombosis that the 30-day stroke recurrence rate was significantly lower under UFH treatment compared to that using anti-Xa agents (4% vs. 31%, p = 0.008). Since the subcutaneous injection formulation of heparin allows for at-home management, consideration should be given to heparin use in cases of cancer-related stroke based on the patient's general condition and underlying disease status.

Conclusion

Cancer-associated stroke has various etiologies, including stroke caused by cancer-related hypercoagulability, coincident stroke with common etiologies, stroke associated with cancer therapy, and others. Notably, thrombi of stroke caused by cancer-related hypercoagulability might exhibit unique characteristics, which can be primarily attributed to their platelet-rich, erythrocyte-poor nature, rendering them difficult to be retrieved. Therefore, judicious selection of the appropriate thrombectomy technique for stroke patients with active cancer might be aided by preprocedural imaging and serum biomarkers, including HVS/SVS, three-territory sign, D-dimer level, and others, to evaluate the stroke subtype and features of the thrombus. Moreover, implementing secondary prevention treatments tailored to the stroke mechanism is crucial for improving the outcomes of stroke patients with active cancer.

Although preprocedural diagnosis, EVT techniques, and secondary preventive treatment for stroke caused by cancer-related hypercoagulability are not yet fully optimized, neurointerventionalists should always consider the underlying mechanisms and carefully evaluate treatment indications and techniques on an individual basis when approaching the treatment for acute stroke patients with active cancer (cancer-associated stroke).

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Disclosure Statement

The author declares that there are no conflicts of interest.

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