Subcutaneous Heparin Therapy for Patients with Cancer-Associated Stroke

Hiroyuki Kawano, MD,*,† Yuko Honda, MD,*,† Tatsuo Amano, MD,*,† Haruko Okano, MD,*,§ Rieko Suzuki, MD,*,† Masataka Torii, MD,*,‡ Yoshiko Unno, MD,*,† Yoshiaki Shiokawa, MD,*,‡ and Teruyuki Hirano, MD*,†

Background: Anticoagulation therapy, particularly subcutaneous heparin therapy, is recommended for cancer-associated thrombosis. However, not starting or discontinuing anticoagulation was not rare. The aim of the present study was to examine the practical issues related to anticoagulation therapy and effects of subcutaneous heparin therapy for cancer-associated stroke. *Methods:* Patients with cancer-associated stroke in our stroke center between October 2014 and August 2017 who were diagnosed as having acute ischemic stroke based on diffusion-weighted imaging were retrospectively enrolled. Baseline clinical characteristics, heparin injection, reasons for no subcutaneous heparin therapy, and clinical outcomes were collected. *Results:* A total of 59 patients with cancer-associated stroke (75 ± 10 years old, male 42%) were enrolled. Lung cancer was the most frequently observed cancer (n = 17, 29%), followed by gastric cancer (n = 8, 14%) and pancreatic cancer (n = 8, 14%). Of the 19 patients (32%) who underwent subcutaneous heparin therapy, it was discontinued in 9 (47%), mainly because of patients' medical conditions (deterioration of cancer or hemorrhagic complication). Ten patients with long-term subcutaneous heparin therapy did not have stroke recurrence. In contrast, among nine patients who discontinued subcutaneous heparin therapy, three (33%) had recurrence of ischemic stroke. Of the 40 patients without subcutaneous heparin therapy, the main reasons for no subcutaneous heparin therapy were the patients' medical conditions (n = 22, 55%). *Conclusions:* Although subcutaneous heparin therapy was given to only one third of cancer-associated stroke patients, long-term subcutaneous heparin therapy might prevent recurrence of cancer-associated stroke.

Key Words: Stroke—cancer—anticoagulation—heparin

Introduction

Ischemic stroke is common in patients with cancer.[1-3] Previous studies showed that 15% of patients with cancer had cerebrovascular disease,[1] and that 4.3% of patients were diagnosed as having cancer after a stroke.[4] Hypercoagulability due to cancer plays an important role in cancer-associated stroke,[5-7] and it was associated with poor survival after stroke in patients with cancer,[8] Anticoagulation therapy is recommended for cancer-associated thrombosis.[9] However, long-term maintenance on anticoagulation therapy, such as subcutaneous or intravenous heparin therapy, is not practical because of hemorrhagic complications and other medical or social conditions. There is a lack of data on the reasons for

From the *Stroke Center, Kyorin University, Mitaka, Tokyo, Japan; †Department of Stroke and Cerebrovascular Medicine, Kyorin University, Mitaka, Tokyo, Japan; ‡Department of Neurosurgery, Kyorin University, Mitaka, Tokyo, Japan; and §Department of Neurology, Kyorin University, Mitaka, Tokyo, Japan.

Received July 19, 2018; revision received September 26, 2018; accepted October 9, 2018.

Financial Disclosure: None.

Address correspondence to Hiroyuki Kawano, MD, PhD, Department of Stroke and Cerebrovascular Medicine, Kyorin University, 6-20-2, Mitaka, Tokyo 181-8611, Japan E-mail: hkawanoo@gmail.com.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.10.012

not starting or discontinuing long-term anticoagulation therapy in patients with cancer-associated stroke.

The aims of the present study were to examine the practical issues related to anticoagulation therapy for cancer-associated stroke and to evaluate whether anticoagulation therapy can reduce stroke recurrence or improve stroke survival.

Methods

Patients

This retrospective observational study evaluated cancer-associated stroke patients in our stroke center between October 2014 and August 2017. The Institutional Review Board in our institute approved this study. Written, informed consent was waived due to the retrospective nature of the study. The inclusion criteria were 1) acute ischemic stroke documented based on diffusion-weighted MRI imaging (DWI) within 7 days after symptom onset; 2) admitted to or sought consultation for acute stroke; and 3) known or newly diagnosed active cancer at the time of stroke diagnosis, after stroke, or during hospitalization. Active cancer was defined as a diagnosis of or treatment for cancer during the 6 months preceding the stroke diagnosis or newly diagnosed cancer, or the presence of recurrent or metastatic cancer. Patients with primary central nervous system tumors were excluded.

Clinical Assessments

The following patient characteristics were retrospectively obtained from medical records: age, sex, and vascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking habits, the National Institutes of Health Stroke Scale (NIHSS) scores on admission and at discharge, the modified Rankin Scale (mRS) score at discharge, and 1-month survival status. Recurrence of ischemic stroke was defined as a symptomatic ischemic stroke identified on DWI. Routine evaluations included brain magnetic resonance imaging (MRI) and MR angiography, electrocardiography, echocardiography, 24-h Holter monitoring, and carotid ultrasonography. Based on the neurological, radiological, cardiological, and hematological profiles (eg, blood counts and D-dimer levels), the stroke subtype was determined according to the criteria of the Trial of Org 10172 in the Acute Stroke Treatment (TOAST) subtype classification system[10] by a consensus of stroke neurologists. If the patients had both active cancer and conventional stroke mechanism, we considered that either has more influence on stroke, and decided the final diagnosis of stroke mechanism by consensus of more than three stroke neurologists based on the neurological, radiological, cardiological, and hematological profiles.

Blood tests, including D-dimer levels, were measured in patients with acute ischemic stroke in the emergency department. For patients with in-hospital stroke, the blood tests were performed immediately after MRI studies. D-dimer data were also obtained at 8 ± 6 days after antithrombotic therapy.

Because of the retrospective nature of the study, the treatment strategy was dependent on the attending stroke neurologists' decision based on the stroke mechanism and the individual patient's condition. Anticoagulation therapy with an adjusted dose of continuous intravenous unfractionated heparin or twice-daily subcutaneous heparin calcium was generally considered first-line treatment. Long-term maintenance on low-molecular-weight heparin (LMWH) for cancer-associated thrombosis is not approved in Japan.

The reasons for not starting or discontinuing heparin included the patient's medical condition (eg, palliative care, multiple metastases, hemorrhagic complication, cardiorespiratory instability), the patient's social condition (eg, transfer to other facility in which patients cannot be treated with heparin), finally diagnosed as a stroke mechanism other than cancer-associated stroke, and the patient's or family's choice (refused maintenance heparin therapy).

Statistical Analysis

The rate of stroke recurrence was compared between long-term subcutaneous heparin, the discontinuation of subcutaneous heparin, maintenance on continuous heparin, and not starting subcutaneous heparin groups using chi-square test. One-month survival after stroke onset was compared between the long-term subcutaneous heparin therapy and the discontinuation group using Fisher's exact test. D-dimer levels were compared between patients with and without pre-stroke anticoagulation, between patients with and without symptomatic stroke recurrence, and between 1-month survivors and nonsurvivors using Fisher's exact test or the Wilcoxon rank sum test. Values $<.05$ were considered significant. The diagnostic value of D-dimer levels for predicting 1-month survival was determined using receiver operating characteristic (ROC) curve analysis. Statistical analyses were performed using the JMP 10 package (SAS Institute Inc., Cary, NC).

Results

In this study, 59 patients with suspected cancer-associated stroke (male 42%; 75.5 ± 10.4 years old; median NIHSS score 3; Table 1) were evaluated. Lung cancer was the most frequent cancer (n = 17, 29%), followed by gastric cancer (n = 8, 14%) and pancreatic cancer (n = 8, 14%). Adenocarcinoma cancer histology was common (n = 49, 83%). Most patients (n = 49, 83%) were diagnosed with cancer prior to the stroke, and 17% (n = 10) of patients were diagnosed with cancer after the stroke. One third of patients received anticoagulation therapy before stroke by reasons of atrial fibrillation (n = 11), deep vein thrombosis (n = 11), and previous ischemic stroke (n = 5). The 1-month survival rate after stroke was 83%.

Of the 59 patients, 47 (80%) underwent continuous intravenous heparin therapy. Subcutaneous heparin therapy was

Table 1. *Patients' characteristics.*

Age, years, mean ± SD	75.5 ± 10.4
Male, *n* (%)	25 (42)
Previous history	
Hypertension	37 (63)
Dyslipidemia	20 (34)
Diabetes	13 (22)
Atrial fibrillation	13 (22)
Deep vein thrombosis	17 (29)
Current smoking	23 (39)
Premorbid mRS score, median (IQR)	1 (0-2)
Baseline NIHSS score	3 (1-7)
mRS score at discharge	3 (1-5)
1-month survival after stroke	49 (83)
Cancer characteristics	
Cancer location	
Lung	17 (29)*,†,‡
Stomach	8 (14)
Pancreas	8 (14)§
Colorectum	6 (10)*
Breast	4 (7)†
Bile duct	3 (5)
Ovary	3 (5)
Prostate	3 (5)‡
Esophagus	2 (3)§
Bladder	3 (5)
Uterus	2 (3)
Hematological	2 (3)
Kidney	1 (2)
Vulva	1 (2)
Unknown	1 (2)
Adenocarcinoma	49 (83)
Diagnosis of cancer after stroke	10 (17)
Prestroke treatment	
Anticoagulation	18 (31)
Warfarin	5
Edoxaban	7
Rivaroxaban	4
Apixaban	1
Intravenous heparin	1
Antiplatelets	7 (12)
Pretreatment D-dimer (*n* = 56), mean ± SD, median (IQR) (μg/mL)	8.9 ± 11.3, 3.9 (1.0-15.1)
D-dimer at 8 ± 6 days after treatment (*n* = 38) (μg/ml)	3.2 ± 3.1, 1.9 (1.0-4.7)
D-dimer level decrease (*n* = 38)	6.8 ± 10.8, 2.3 (.4-12.4)
Stroke treatment	
Continuous intravenous heparin	47 (80)
Subcutaneous heparin after continuous intravenous heparin	19 (32)

Abbreviations: IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SD, standard deviation;.

*Includes one patient with lung and colorectal cancer.

†Includes one with lung and breast cancer.

‡ Includes one with lung and prostatic cancer.

§Includes one with esophageal and pancreatic cancer.

started in 19 (32%) patients after continuous intravenous heparin therapy. The mean (standard deviation, SD) dosages of continuous intravenous heparin and subcutaneous heparin therapy were 13,437 (5351) units and 15,800 (4250) units per day, respectively. No patients developed heparin-induced thrombocytopenia. The subcutaneous heparin therapy was given by the patient's family (*n* = 8, 42%), the patient (*n* = 7, 37%), or nurses (*n* = 4, 21%). Of the 19 patients who were treated with subcutaneous heparin, it was discontinued in 9 patients (47%) because of the patient's medical condition (*n* = 6; exhaustion, 2; hemorrhagic complication, 2; cardiorespiratory instability, 2; curative operation, 1), mental stress associated with subcutaneous heparin injection (*n* = 2), pain at the injection site (*n* = 1), and the physical difficulty of heparin injection (*n* = 1, Table 2). Among nine patients who discontinued subcutaneous heparin therapy, three (33%) had recurrence of ischemic stroke (follow-up period, median 96 days, range 30-300 days). Ten patients on long-term subcutaneous heparin therapy did not have stroke recurrence (follow-up period, 87 days, range 4-787 days). There was no significant difference in follow-up period between patients who discontinued and continued subcutaneous heparin ($p = .51$). The recurrence rates of ischemic stroke were lower in patients with long-term subcutaneous heparin than in those discontinued subcutaneous heparin therapy, maintenance on continuous heparin, or not starting subcutaneous heparin groups (0%, 33%, 20%, and 3%, respectively, $p = .02$, Figure 1). There was no significant difference in 1-month survival between patients with and without subcutaneous heparin therapy (100% vs. 89%, $p = .47$).

Forty patients (68%) were not treated with subcutaneous heparin therapy. Reasons for no subcutaneous heparin therapy were patients' medical condition (*n* = 22, 55%; palliative care, 10; multiple metastases, 10; hemorrhagic complications, 9; cardiorespiratory instability, 8), final diagnosis of conventional stroke mechanism other than cancer-associated stroke (*n* = 11, 27%), patient's or family's choice (*n* = 3, 8%), and difficulty with subcutaneous heparin injection in the transferred facility (*n* = 3, 8%, Table 3).

D-dimer levels at pretreatment and 8 ± 6 days after treatment were obtained in 55 and 38 patients, respectively. The median D-dimer levels at pretreatment and 8 ± 6 days after treatment were 3.9 μg/mL (interquartile range, IQR, 1.0-15.1) and 1.9 μg/ml (IQR 1.0-4.7), respectively. The pretreatment D-dimer level was significantly higher in patients with adenocarcinoma than in those with nonadenocarcinoma (median, 6.6 μg/mL vs. 1.0 μg/ml, $p = .04$). Prestroke anticoagulation therapy was not associated with pretreatment D-dimer levels (median, 3.6 μg/mL vs. 6.6 μg/ml, $p = .53$). Pretreatment D-dimer levels were significantly lower in 1-month survivors than others (median, 2.6 μg/mL vs. 15.2 μg/ml, $p = .01$). D-dimer levels at 8 ± 6 days after treatment were also significantly lower in 1-month survivors (1.8 μg/mL vs. 5.4 μg/ml, $p = .03$). The ROC curve analyses showed that D-dimer levels at pretreatment and 8 ± 6 days after treatment were significant

Table 2. *Reasons for discontinuation of subcutaneous heparin therapy (n = 9).*

Medical conditions	6
Exhaustion	2
Hemorrhagic complications	2
Cardiorespiratory instability	1
Curative surgery	1
Mental stress of heparin therapy	2
Pain at the injection site	1
Physical difficulty of heparin injection	1
Transfer to other facility in which patients could not be treated with heparin	1

predictors of 1-month survival (area under the curve, AUC = .81, $p = .07$, with an optimal cutoff of 5.03 μg/mL, and AUC = .83, $p = .04$, with an optimal cutoff of 2.77 μg/ml, respectively). D-dimer levels at pretreatment and 8 ± 6 days after treatment were not significantly associated with recurrence of stroke than those without recurrence of stroke (median 11.4 μg/mL vs. 2.9 μg/ml, $p = .44$, and 1.2 μg/mL vs. 1.9 μg/ml, $p = .94$, respectively). There were no significant differences in D-dimer levels at 8 ± 6 days after treatment between patients who did and did not continue long-term subcutaneous heparin therapy (2.29 μg/mL vs. 1.81 μg/ml, $p = .92$).

Definite diagnosis of cancer-associated stroke was difficult, especially in patients with conventional stroke mechanism. To overcome this uncertainty, we reanalyzed our data dividing into patient finally diagnosed of cancer-associated stroke and conventional stroke mechanism other than cancer-associated stroke (Table S1 and Figure S1 in the Supplementary Material).

Discussion

First, the present study found that subcutaneous heparin was given to one third of cancer-associated stroke patients, and the reasons for not giving heparin therapy for cancer-associated stroke were identified. Second, it was found that long-term subcutaneous heparin therapy might prevent recurrence of cancer-associated stroke.

Anticoagulation therapy is recommended for cancer-associated thrombosis.[9] In our institute, we generally consider heparin therapy for cancer-associated stroke. However, the actual rate of heparin therapy for cancer-associated stroke was lower than expected. The main reason for discontinuation of or not starting subcutaneous heparin therapy was the presence of medical conditions, such as deterioration of cancer (palliative care and/or multiple metastases) or hemorrhagic complications. In such patients, abandonment of heparin therapy might be inevitable. Subcutaneous heparin therapy is burdensome due to the daily subcutaneous injections because of the physical and mental stress related to the injections, which might limit adoption of long-term therapy and lead to the patient's or the family's decision to refuse maintenance heparin therapy. Another reason for not giving heparin therapy was social, when there was difficulty in heparin injection after discharge from the stroke unit. Such social problems might be overcome by developing and establishing the evidence for heparin therapy or other therapies

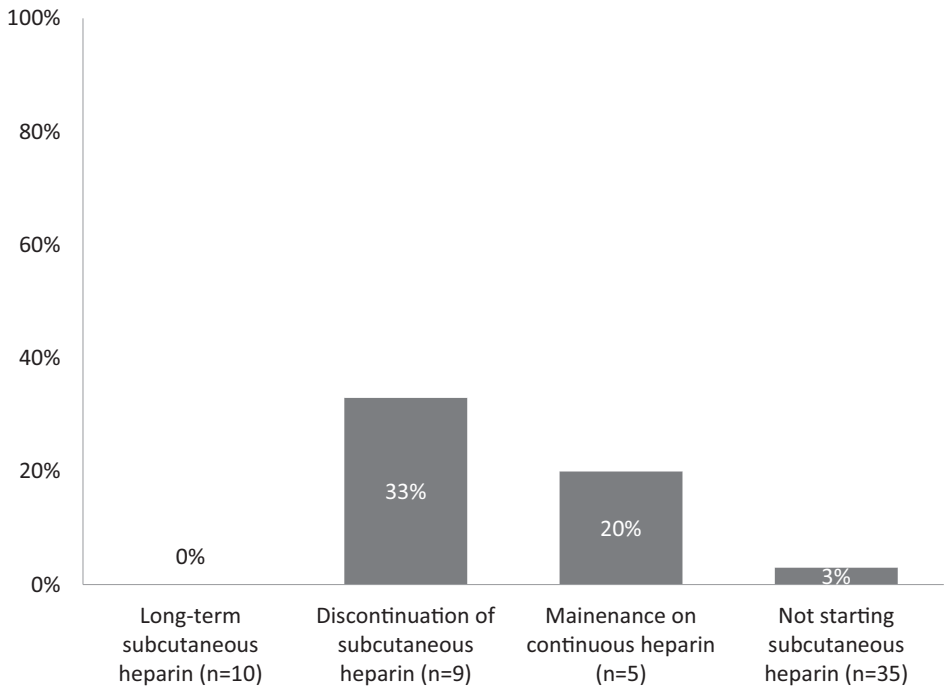

Figure 1. *The recurrence rates of ischemic stroke were lower in patients with long-term subcutaneous heparin than in those discontinued subcutaneous heparin therapy, maintenance on continuous heparin, or not starting subcutaneous heparin groups (0%, 33%, 20%, and 3%, respectively,* p = .02*).*

Table 3. *Reasons for not starting subcutaneous heparin therapy (n = 40).*

Medical conditions	22
Palliative care	10
Multiple metastasis	10
Hemorrhagic complications	9
Cardiorespiratory instability	8
Death before subcutaneous heparin could be started	4
Thrombocytopenia	3
Severe disability due to stroke	2
Excessively prolonged activated partial thromboplastin time	1
Maintenance on continuous heparin therapy	5
Final stroke mechanism other than cancer-associated stroke	11
Large artery atherosclerosis	3
Cardioembolism	2
Other causes (aortogenic embolism, arterial dissection, chemotherapy induced, antiplatelet drug discontinuation)	1 each
Unknown	2
Patient's or family's choice (refused maintenance heparin therapy)	3
Transfer to other facility in which patients could not be treated with heparin	3

(eg, direct oral anticoagulant agents, DOACs) for cancer-associated stroke in the future.

The present results suggested that long-term heparin therapy might prevent stroke recurrence. No patients on long-term subcutaneous heparin therapy had stroke recurrence, although one third of patients who discontinued subcutaneous heparin had recurrence of ischemic stroke. Avoiding recurrence of stroke can lead to maintenance of patients' quality of life during their lifetime. Long-term heparin therapy is recommended to prevent recurrence of stroke in patients with cancer-associated stroke if the patient's medical and social conditions allow it. To reduce the burden of heparin injection, oral anticoagulants might be an alternative. The present data do not suggest that oral anticoagulants were not effective for stroke prevention, because the study had a small sample size and was not mainly focused on the effects of oral anticoagulants, although one third of patients had prestroke anticoagulation. A recent study reported the noninferiority of oral edoxaban compared with subcutaneous LMWH for cancer-associated thrombosis with respect to the composite outcome of recurrent venous thromboembolism or major bleeding.[11] Large prospective, randomized trials are needed to determine whether heparin therapy or DOACs can prevent recurrence of cancer-associated stroke without increasing bleeding.

The plasma D-dimer levels before and after heparin treatment were associated with 1-month survival. This result is consistent with a previous study,[8] which reported that the successful correction of hypercoagulability was significantly associated with 1-year survival.[8] An elevated D-dimer level is associated with diagnosis and treatment response in cancer-associated stroke.[2,7,12-14] The D-dimer level might be useful for predicting patient prognosis. However, the D-dimer level after treatment does not represent the most appropriate level in patents with heparin therapy, because the therapeutic target value of D-dimer levels was not set. Previous papers used D-dimer levels,[8,15] which did not represent the therapeutic target level.

The present study has several limitations. First, the study could not show that the D-dimer level was associated with recurrence of symptomatic stroke, which might be caused by several factors, including small sample size, intensity of anticoagulation, cancer activity, or other thromboembolism. Second, regarding stroke recurrence, only symptomatic ischemic stroke was evaluated. Autopsy studies demonstrated that the majority of cancers associated with cerebral infarction were asymptomatic.[1] Therefore, the rate of stroke recurrence might have been underestimated in the present study. Third, subcutaneous heparin therapy was not associated with 1-month survival. The follow-up period might have been too short to adequately evaluate the effect of heparin therapy. Fourth, because long-term maintenance on LMWH for cancer-associated thrombosis, which has been recommended,[9] is not approved in Japan, patients on LMWH were not included in this study. Fourth, no association between cancer-associated stroke and treatment for cancer was found. Further studies are needed to show whether D-dimer levels after subcutaneous heparin therapy can predict both symptomatic and asymptomatic stroke recurrence, or survival in patients with cancer-associated stroke. Finally, if patients had both active cancer and conventional stroke mechanism, it is very difficult to definitely distinguish cancer-associated stroke and conventional stroke mechanism other than cancer-associated stroke.

Conclusions

Long-term subcutaneous heparin therapy might prevent recurrence of cancer-associated stroke although subcutaneous heparin therapy was given to only one third of patients with cancer-associated stroke. The reason for not starting subcutaneous heparin therapy was mainly patients' medical conditions. How to prevent stroke and improve clinical outcomes in patients with hemorrhagic complications or deterioration of cancer remains to be established.

Supplementary Materials

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2018.10.012.

References

1. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine 1985;64:16-35.
2. Kim SG, Hong JM, Kim HY, et al. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. Stroke 2010;41:798-801.
3. Navi BB, Singer S, Merkler AE, et al. Recurrent thromboembolic events after ischemic stroke in patients with cancer. Neurology 2014;83:26-33.
4. Selvik HA, Thomassen L, Bjerkreim AT, et al. Cancer-associated stroke: the Bergen NORSTROKE Study. Cerebrovasc Dis Extra 2015;5:107-113.
5. Schwarzbach CJ, Schaefer A, Ebert A, et al. Stroke and cancer: the importance of cancer-associated hypercoagulation as a possible stroke etiology. Stroke 2012;43:3029-3303.
6. Bang OY, Seok JM, Kim SG, et al. Ischemic stroke and cancer: stroke severely impacts cancer patients, while cancer increases the number of strokes. J Clin Neurol 2011;7:53-59.
7. Seok JM, Kim SG, Kim JW, et al. Coagulopathy and embolic signal in cancer patients with ischemic stroke. Ann Neurol 2010;68:213-219.
8. Lee MJ, Chung JW, Ahn MJ, et al. Hypercoagulability and mortality of patients with stroke and active cancer: the OASIS-CANCER Study. J Stroke 2017;19:77-87.
9. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315-352.
10. Adams Jr HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke 1993;24:35-41.
11. Raskob GE, van Es N, Verhamme P, et al. Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-624.
12. Kim SJ, Park JH, Lee MJ, et al. Clues to occult cancer in patients with ischemic stroke. PLoS One 2012;7:e44959.
13. Finelli PF, Nouh A. Three-territory DWI acute infarcts: diagnostic value in cancer-associated hypercoagulation stroke (Trousseau syndrome). AJNR Am J Neuroradiol 2016;37:2033-2036.
14. Cestari DM, Weine DM, Panageas KS, et al. Stroke in patients with cancer: incidence and etiology. Neurology 2004;62:2025-2030.
15. Toh CH, Hoots WK. The scoring system of the scientific and standardisation committee on disseminated intravascular coagulation of the international society on thrombosis and haemostasis: a 5-year overview. J Thromb Haemost 2007;5:604-606.