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ORIGINAL RESEARCH

Distinction in Prevalence of Atherosclerotic Embolic Sources in Cryptogenic Stroke With Cancer Status

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BACKGROUND: Cerebrovascular diseases are common comorbidities in patients with cancer. Although active cancer causes ischemic stroke by multiple pathological conditions, including thromboembolism attributable to Trousseau syndrome, the relationship between stroke and inactive cancer is poorly known. The aim of this study was to elucidate the different underlying pathogeneses of cryptogenic stroke in active and inactive patients with cancer, with detailed investigation by transesophageal echocardiography.

METHODS AND RESULTS: CHALLENGE ESUS/CS (Mechanisms of Embolic Stroke Clarified by Transesophageal Echocardiography for Embolic Stroke of Undetermined Source/Cryptogenic Stroke) registry is a multicenter registry including data of patients initially diagnosed as having cryptogenic stroke and undergoing transesophageal echocardiography. Patients were divided into active cancer, inactive cancer, and noncancer groups, and their clinical features were compared. Of the total 667 enrolled patients (age, 68.7±12.8 years; 455 men), 41 (6.1%) had active cancer, and 51 (7.5%) had a history of inactive cancer. On multinomial logistic regression analysis, infarctions in multiple vascular territories (odds ratio [OR], 2.73; 95% CI, 1.39–5.40) and CRP (C-reactive protein) (OR, 1.10; 95% CI, 1.01–1.19) were independently associated with active cancer, whereas age (OR, 1.05; 95% CI, 1.01–1.08), contralateral carotid stenosis from the index stroke lesion (OR, 4.05; 95% CI, 1.60–10.27), calcification of the aortic valve (OR, 2.10; 95% CI, 1.09–4.05), and complicated lesion of the aortic arch (OR, 2.13; 95% CI, 1.11–4.10) were significantly associated with inactive cancer.

CONCLUSIONS: Patients with cancer were not rare in cryptogenic stroke. Although patients with active cancer had more multiple infarctions, patients with inactive cancer had more atherosclerotic embolic sources potentially causing arteriogenic strokes.

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Key Words: atherosclerosis ■ cancer ■ cryptogenic stroke ■ embolic stroke of undetermined source ■ transesophageal echocardiography

Stroke is a common comorbidity in patients with cancer. A postmortem study reported that 15% of patients with cancer had cerebrovascular diseases.[1] In addition, recent national surveillance data from the United States showed that the risk of stroke for patients with cancer was more than twice that of the general population.[2] More important, the mechanisms and pathological characteristics of stroke in patients

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CLINICAL PERSPECTIVE

What Is New?

- Patients with cryptogenic stroke had various pathogenesis and embolic sources according to their cancer status.
- Patients with cryptogenic stroke with comorbidity of active cancer had infarctions in multiple vascular territories more frequently than patients with inactive cancer.
- On the contrary, detailed investigation of transesophageal echocardiography elucidated that the patients with cryptogenic stroke with inactive cancer had more potential atherosclerotic embolic sources for their stroke.

What Are the Clinical Implications?

- Infarctions in multiple vascular territories of patients with active cancer might suggest the coexistence of intravascular coagulopathy regarded as Trousseau syndrome.
- Meanwhile, atherosclerosis of patients with inactive cancer could be partly related to antineoplastic treatment, such as chemotherapy and radiation.
- Differences in mechanisms identified in patients with active compared with inactive cancer may result in different secondary stroke prevention strategies in individual patients.

Nonstandard Abbreviations and Acronyms

ACL	aortic complicated lesion
CS	cryptogenic stroke
ESUS	embolic stroke of undetermined source
TEE	transesophageal echocardiography

with cancer are definitely diverse.[1–3] As examples, direct invasion of tumor cells,[1,2] concurrent coagulopathy,[1–4] coexisting and de novo atrial fibrillation,[3,5] and atherosclerotic change[3,6] could be possible culprits in patients with cancer-associated stroke. In particular, thromboembolism attributable to coagulopathy, called Trousseau syndrome, was regarded as a major component of ischemic stroke associated with active and advanced cancer.

Trousseau syndrome was first described in 1865 by Armand Trousseau as an unpredictable thrombophlebitis associated with occult visceral malignancy.[7] The term was then refined in 1977 to describe chronic disseminated intravascular coagulopathy associated with microangiopathy, verrucous nonbacterial thrombotic endocarditis, and arterial emboli in patients with cancer, especially mucin-positive carcinomas.[8] In recent times, the term has been used in various clinical settings for any kind of coagulopathy occurring in the setting of any malignancy,[9] and it was emphasized that it accounted for a notable proportion of cryptogenic stroke (CS) cases.[3,4,10] Meanwhile, little is known about the relationship between stroke and inactive cancer. A previous study reported that childhood cancer survivors, especially those treated with radiation therapy and alkylating agents, had an increased risk of late-occurring stroke.[11] In addition, the risk of stroke increased with time for almost all cancer survivors.[2] Although recent advances in multidisciplinary antineoplastic treatment have increased the survival rate of patients with cancer, cardiovascular death among cancer survivors has increased.[12,13] Thus, it is an urgent priority to elucidate the pathophysiological features of stroke associated with not only active, but also inactive, cancers in the era of cancer survivors.[12]

In addition, a pragmatic concept of CS, embolic stroke of undetermined source (ESUS), which also includes covert nonbacterial thrombotic endocarditis and tumor emboli from occult cancer as essential possible embolic sources of CS, has been advocated.[14] CS and ESUS should definitely encompass these classic causes as potential embolic sources. CS is one of the most frequent stroke subtypes in patients with cancer,[3,4,10,15] and cancer-associated ischemic stroke is frequently recurrent.[16] Thus, it is crucial to identify the exact pathophysiological features and embolic sources of cancer-associated patients with CS for the purpose of providing optimal secondary prophylaxis.

In the present study, a multicenter registry with a comprehensive database of patients initially classified as having CS and undergoing transesophageal echocardiography (TEE) to elucidate their latent embolic causes was created. Using this multicenter TEE registry, the aim of this study was to clarify the frequency and clinical features of patients with active and inactive cancer with CS. In addition, the latent pathological differences, especially in embolic origins, were investigated in patients with CS with active and inactive cancers.

METHODS

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Study Population

The CHALLENGE ESUS/CS (Mechanisms of Embolic Stroke Clarified by Transesophageal Echocardiography for Embolic Stroke of Undetermined Source/Cryptogenic Stroke) registry,

a retrospective, multicenter registry enrolling consecutive patients originally diagnosed as having CS and undergoing TEE in 8 hospitals in Japan between April 2014 and December 2016, was constructed. Inclusion criteria for this registry were as follows: (1) within 7 days of stroke onset; (2) nonlacunar stroke on neuroradiological imaging; (3) absence of arterial stenosis ≥50% or occlusion in a corresponding large artery; (4) absence of major emboligenic cardiac diseases; and (5) absence of other determined stroke causes. As exclusion criteria, the diagnostic criteria of ESUS recommended cardiac monitoring for >24 hours; therefore, atrial fibrillation that was detected at <24 hours after admission was excluded from the CHALLENGE ESUS/CS registry. Institutional review boards in all 8 participating centers approved the protocol. Clinical information was obtained from medical records, and the need to obtain written, informed consent from each patient was therefore waived in this retrospective study. The present study was registered at http://www.umin.ac.jp/ctr/ (UMIN000032957).

TEE Study

Subjects were awake and had fasted for at least 4 hours before TEE. Lidocaine spray was given, but no premedication was given. To investigate the heart and aortic arch, a multiplane probe was manipulated to provide appropriate views, including axial and sagittal images. An atrial septal aneurysm was diagnosed when the atrial septum extended into the left or right atrium, or both. The presence of a right-to-left shunt was assessed by injecting agitated saline and making subjects perform the Valsalva maneuver, and then the numbers of microbubbles with and without contrast agent were compared. The number of microbubbles passing from the right atrium to the left atrium was also counted. A patent foramen ovale was diagnosed when microbubbles were visualized in the left atrium within 3 cardiac cycles after the Valsalva maneuver. A pulmonary arteriovenous fistula was diagnosed when microbubbles were visualized in the left atrium >3 cardiac cycles after the Valsalva maneuver or when microbubbles were visualized without the Valsalva maneuver. Plaque thickness ≥4 mm, mobile plaque seen swinging on their peduncle, or ulcerative plaque with width and maximum depth of at least 2 mm each was defined as aortic complicated lesion (ACL). Examinations were performed by 2 or 3 experienced sonographers in each facility.

Magnetic Resonance Imaging Sequences

Magnetic resonance imaging scans were performed at each institution on 1.5- or 3-T scanners during hospitalization. Sequences included axial diffusion-weighted imaging, fluid-attenuated inversion recovery imaging, magnetic resonance angiography, and the gradient-recalled echo (GRE) T2* sequence. Diffusion-weighted imaging (repetition time/echo time=3000–8000/60–91 ms) was used to assess the size and distribution of the index stroke lesion. A large infarct was defined as >3 cm in diameter. The distribution of the index lesions was divided into single and multiple vascular territories among bilateral anterior, middle, and posterior cerebral arteries, and cortical and subcortical lesions. Fluid-attenuated inversion recovery imaging (repetition time/echo time=9000–12 000/94–120 ms) was used to evaluate the degree of deep and subcortical white matter hyperintensity and periventricular hyperintensity and classified as Fazekas grades 0 to 3. Magnetic resonance angiography (repetition time/echo time=19–37/2.8–7.5 ms) was used to detect intracranial stenosis >50%, principally not relevant to the infarction area. GRE T2* (repetition time/echo time=410–740/12–20 ms) was used to identify cerebral microbleeds, defined as a rounded area of signal loss with diameter <10 mm. The size and distribution of stroke lesions, the degree of deep and subcortical white matter hyperintensity and periventricular hyperintensity, the existence of intracranial stenosis, and the presence of cerebral microbleeds were all assessed by several experienced neurologists in each institution.

Data Collection and Analyses

Baseline clinical information, including cardiovascular risk factors, history and status of cancer, laboratory and radiological data on admission, echocardiographic findings, and clinical course on admission, was collected by hospital chart or database reviews during the study period from May 2017 to July 2019. The definitions of cardiovascular risk factors were described in our previous work.[17,18] Covert atrial fibrillation >24 hours after admission was detected by continuous cardiac monitoring, 24-hour Holter electrocardiography, or, infrequently, an insertable cardiac monitor. Baseline characteristics, radiological and laboratory data, echocardiographic findings, including potential embolic diseases, and clinical courses were compared by cancer status (none, active, or inactive).

On the basis of previous studies,[15,19] active cancer was defined as cancer diagnosed or under treatment within 6 months before index stroke onset or detected on imaging examination and newly diagnosed during hospitalization. On the other hand, inactive cancer was defined as cancer treated within >6 months before stroke onset, and remission or complete recovery was confirmed at the time of admission without any evidence of active cancer on imaging investigation during the hospital stay.

Statistical Analysis

Numerical values are reported as means±SD or medians with interquartile range. Data were analyzed using the Kruskal-Wallis test for nonparametric analyses and the χ^2 test and Fisher exact test for categorical variables, as appropriate. All variables related to baseline clinical characteristics and imaging and laboratory data with values of $P<0.05$ on univariate analyses were entered into multinomial logistic regression analyses to identify independent variables related to the pathophysiological status of cancer. A 2-sided probability value of $P<0.05$ was considered significant. All data were analyzed using SPSS for Macintosh version 26.0 software (SPSS, Chicago, IL).

RESULTS

A total of 677 patients initially classified as having CS were enrolled in the present study. Their mean age was 68.7±12.8 years, and 455 men were

Table 1. Baseline Characteristics, Cardiovascular Risks, MRI and TEE Findings, and Laboratory Data of Patients With Active and Inactive Cancers

Variable	Noncancer group (n=585; 86.4%)	Active cancer group (n=41; 6.1%)	Inactive cancer group (n=51; 7.5%)	*P* value
Age, y	68.0±13.0	70.7±11.1	75.7±8.6	<0.001
Men	391 (66.8)	24 (58.5)	40 (78.4)	0.114
Premorbid mRS score 0–2	553 (94.5)	41 (100.0)	46 (90.2)	0.100
Hypertension	417 (71.3)	28 (68.3)	39 (76.5)	0.657
Diabetes	146 (25.0)	12 (29.3)	14 (27.5)	0.780
Dyslipidemia	295 (50.4)	19 (46.3)	31 (60.8)	0.303
CKD	221 (37.8)	12 (29.3)	19 (37.3)	0.552
Ischemic heart disease	61 (10.4)	2 (4.9)	5 (9.8)	0.520
Previous stroke	104 (17.8)	7 (17.1)	12 (23.5)	0.583
History of smoking	288 (49.2)	18 (43.9)	31 (60.8)	0.211
Prior antiplatelet agents	149 (25.5)	5 (12.2)	14 (27.5)	0.148
Prior anticoagulants	14 (2.4)	3 (7.3)	0 (0.0)	0.102
NIHSS score on admission	2 (1–5)	3 (2–4.5)	3 (1–7)	0.115
DWI lesion size >3 cm*	172 (29.6)	15 (36.6)	14 (28.6)	0.622
Cortical infarction*	460 (79.0)	36 (87.8)	43 (87.8)	0.153
Infarctions in multiple vascular territories*	145 (24.9)	21 (51.2)	15 (30.6)	0.001
DSWMH*	198 (34.0)	17 (41.5)	13 (26.5)	0.327
PVH*	208 (35.7)	17 (41.5)	24 (49.0)	0.152
CMBs†	181 (31.7)	10 (24.4)	18 (36.7)	0.453
Intracranial artery stenosis*	61 (10.5)	5 (12.2)	6 (12.2)	0.884
Contralateral carotid artery stenosis	23 (3.9)	2 (4.9)	8 (15.7)	0.004
Right-to-left shunt‡	270 (47.8)	23 (56.1)	19 (39.6)	0.297
ACL in the aortic arch§	207 (35.5)	14 (34.1)	33 (64.7)	<0.001
Covert atrial fibrillation	58 (9.9)	1 (2.4)	5 (9.8)	0.304
Calcification of aortic valve‖	122 (21.0)	7 (17.1)	24 (47.1)	<0.001
Calcification of mitral valve¶	57 (10.6)	5 (13.5)	7 (14.6)	0.618
WBC count, /μL	7277±2683	7487±2876	7192±2717	0.874
CRP, mg/dL#	0.61±2.33	1.83±2.72	0.60±1.45	<0.001
D-dimer, μg/mL	2.47±16.5	11.4±20.9	2.22±2.64	<0.001

Data are presented as number (percentage), mean±SD, or median (interquartile range). ACL indicates aortic complicated lesion; CKD, chronic kidney disease; CMB, cerebral microbleed; CRP, C-reactive protein; DSWMH, deep and subcortical white matter hyperintensity; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PVH, periventricular hyperintensity; TEE, transesophageal echocardiography; and WBC, white blood cell.

*n=5 missing values.
†n=16 missing values.
‡n=23 missing values.
§n=2 missing values.
‖n=3 missing values.
¶n=53 missing values.
#n=47 missing values.

enrolled. TEE showed that 254 (37.6%) patients had ACL in the aortic arch, 312 (47.7%) had a right-to-left shunt, and 153 (22.7%) had aortic valve calcification, whereas only 2 patients had nonbacterial thrombotic endocarditis. Of the 677 patients with CS, 41 (6.1%) had active cancer, and 51 (7.5%) had a history of inactive cancer.

Cancer Status and Baseline Characteristics, Including Potential Embolic Sources

Baseline characteristics of the 3 groups according to cancer status are shown in Table 1. Whereas the inactive cancer group was the oldest of the 3 groups (noncancer versus active cancer versus inactive cancer, 68.0±13.0 versus 70.7±11.1 versus 75.7±8.6 years; $P<0.001$), other clinical patient background characteristics, including cardiovascular risk factors, were not significantly different among the 3 groups.

As for the imaging examinations, brain magnetic resonance imaging showed that multiple lesions in multiple vascular territories were the most frequent in the active cancer group compared with the other 2 groups (noncancer versus active cancer versus inactive cancer, 24.9% versus 51.2% versus 30.6%; $P=0.001$). Carotid duplex ultrasonography showed that contralateral carotid stenosis from the index stroke lesion was the most common in the inactive cancer group (noncancer versus active cancer versus inactive cancer, 3.9% versus 4.9% versus 15.7%; $P=0.004$) compared with the other 2 groups. In addition, on TEE, ACL in the aortic arch (noncancer versus active cancer versus inactive cancer, 35.5% versus 34.1% versus 64.7%; $P<0.001$) and calcification of the aortic valve (noncancer versus active cancer versus inactive cancer, 21.0% versus 17.1% versus 47.1%; $P<0.001$) were the most frequent in the inactive cancer group.

Laboratory examinations showed that CRP (C-reactive protein) (noncancer versus active cancer versus inactive cancer, 0.61±2.33 versus 1.83±2.72 versus 0.60±1.45 mg/dL; $P<0.001$) and D-dimer (noncancer versus active cancer versus inactive cancer, 2.47±16.5 versus 11.4±20.9 versus 2.22±2.64 mg/dL; $P<0.001$) were the highest in the active cancer group.

On multinomial logistic regression analysis, multiple lesions in multiple vascular territories (odds ratio [OR], 2.73; 95% CI, 1.39–5.40) and CRP (OR, 1.10; 95% CI, 1.01–1.19) were independently associated with active cancer. Age (OR, 1.05; 95% CI, 1.01–1.08), contralateral carotid stenosis (OR, 4.05; 95% CI, 1.60–10.27), ACLs in the arch (OR, 2.13; 95% CI, 1.11–4.10), and calcification of the aortic valve (OR, 2.10; 95% CI, 1.09–4.05) were significantly associated with inactive cancer (Table 2).

Therapy and Clinical Course After Admission

The treatment and prognosis of the 3 groups according to cancer status are presented in Table 3. As secondary prevention, antiplatelet therapy was the least frequent (noncancer versus active cancer versus inactive cancer, 70.1% versus 43.9% versus 76.5%; $P=0.001$), whereas anticoagulant therapy was the most common (noncancer versus active cancer versus inactive cancer, 33.0% versus 56.1% versus 27.5%; $P=0.006$), in the active cancer group. In addition, 2 patients with active cancer died during their hospital stays (noncancer versus active cancer versus inactive cancer, 0% versus 4.9% versus 0%; $P=0.004$).

Primary Lesion, Histological Type, Clinical Stage, and Treatment of Active and Inactive Cancers

First, primary lesions of active and inactive cancers are shown in Figure 1. In both active and inactive cancers, lung cancer was the most prevalent cancer. Prostate cancer was more frequent in the active cancer group, whereas bladder cancer was more common in the

Table 2. Multinomial Logistic Regression Analysis for Predictors Associated With Active and Inactive Cancers

	Active cancer vs none			Inactive cancer vs none		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (per 1 y)	1.03	1.00–1.06	0.067	1.05	1.01–1.08	0.009
Infarctions in multiple vascular territories	2.73	1.39–5.40	0.004	1.16	0.58–2.32	0.669
Contralateral carotid artery stenosis	0.97	0.21–4.41	0.966	4.05	1.60–10.27	0.003
ACL in the aortic arch	0.84	0.41–1.73	0.643	2.13	1.11–4.10	0.024
Calcification of aortic valve	0.65	0.27–1.59	0.347	2.10	1.09–4.05	0.027
CRP	1.10	1.01–1.19	0.029	0.99	0.83–1.19	0.906
D-dimer	1.01	0.99–1.02	0.354	0.96	0.87–1.06	0.439

ACL indicates aortic complicated lesion; CRP, C-reactive protein; and OR, odds ratio.

Table 3. Treatment and Clinical Courses of Patients With Active and Inactive Cancers

Variable	Noncancer group (n=585; 86.4%)	Active cancer group (n=41; 6.1%)	Inactive cancer group (n=51; 7.5%)	*P* value
Antiplatelet therapy on discharge	404 (70.1)	18 (43.9)	39 (76.5)	0.001
Anticoagulant therapy on discharge	190 (33.0)	23 (56.1)	14 (27.5)	0.006
Death on discharge	0 (0.0)	2 (4.9)	0 (0.0)	0.004
Recurrence of stroke	21 (3.6)	4 (9.8)	0 (0.0)	0.054
Any hemorrhagic stroke	57 (9.7)	6 (14.6)	8 (15.7)	0.277

Data are presented as number (percentage).

inactive cancer group. One patient in the active cancer group and 5 patients in the inactive cancer group had double cancers.

Information on cancer histological type and clinical stage were available in 15 (37%) and 20 (49%) cases in the active cancer group, respectively, and 14 (27%) and 10 (20%) cases in the inactive cancer group, respectively (Figure 2). Compared with inactive cancers, adenocarcinoma tended to be more frequent in active cancers. For clinical stage, active cancers were in a more advanced stage, whereas inactive cancers were in an earlier stage. Treatment histories, such as surgery, chemotherapy, and radiotherapy, were available for 28 (68%), 28 (68%), and 23 (56%) patients with active cancer, respectively, and 40 (78%), 17 (33%), and 17 (33%) patients with inactive cancer, respectively (Figure 2).

DISCUSSION

In the present study, the CHALLENGE ESUS/CS registry showed that 6.1% of patients originally diagnosed as having CS had comorbid active cancer, and 7.5% had a history of inactive cancer. Compared with patients with CS who did not have cancer, patients with comorbid active cancer had more infarctions in multiple vascular territories, whereas patients with a history of inactive cancer had more atherosclerotic embolic sources causing arteriogenic strokes.

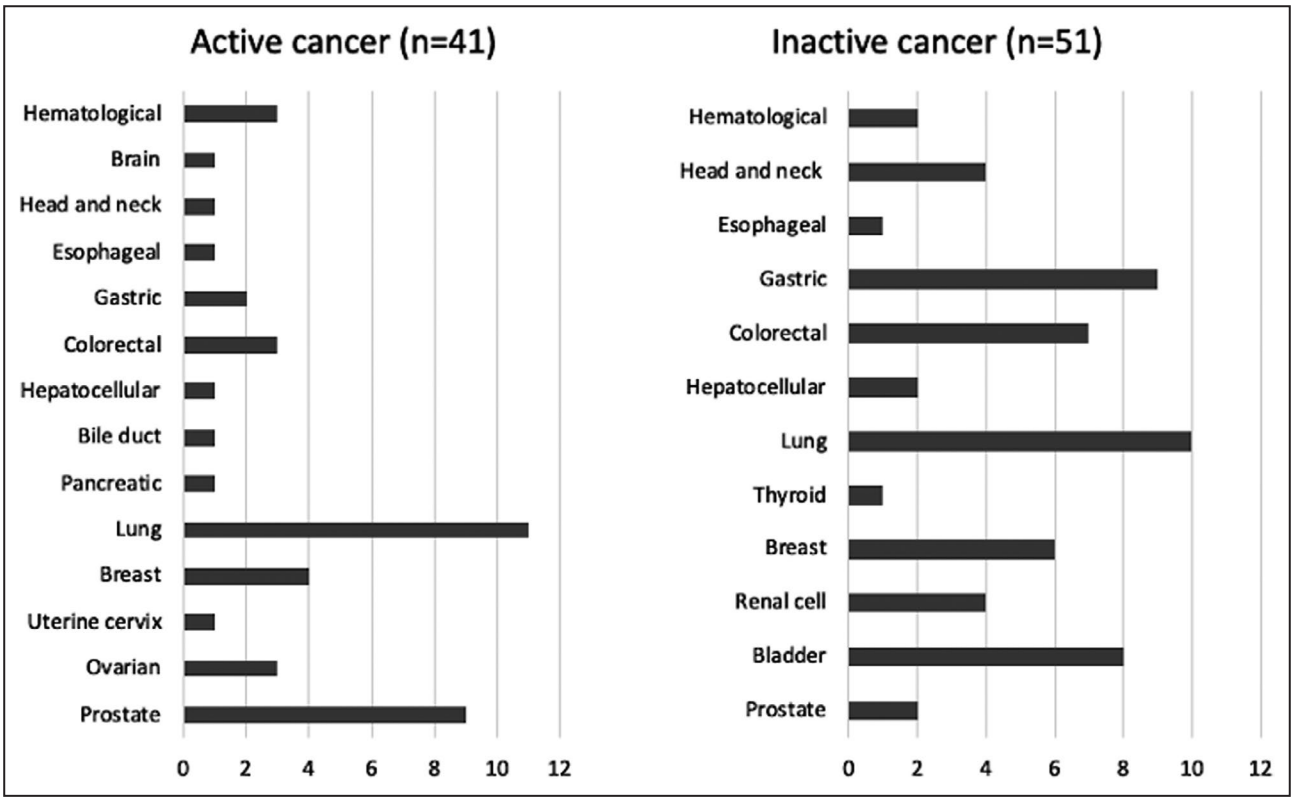

Figure 1. Primary lesions of active and inactive cancers.
The numbers of patients for each primary lesion of active and inactive cancers are presented.

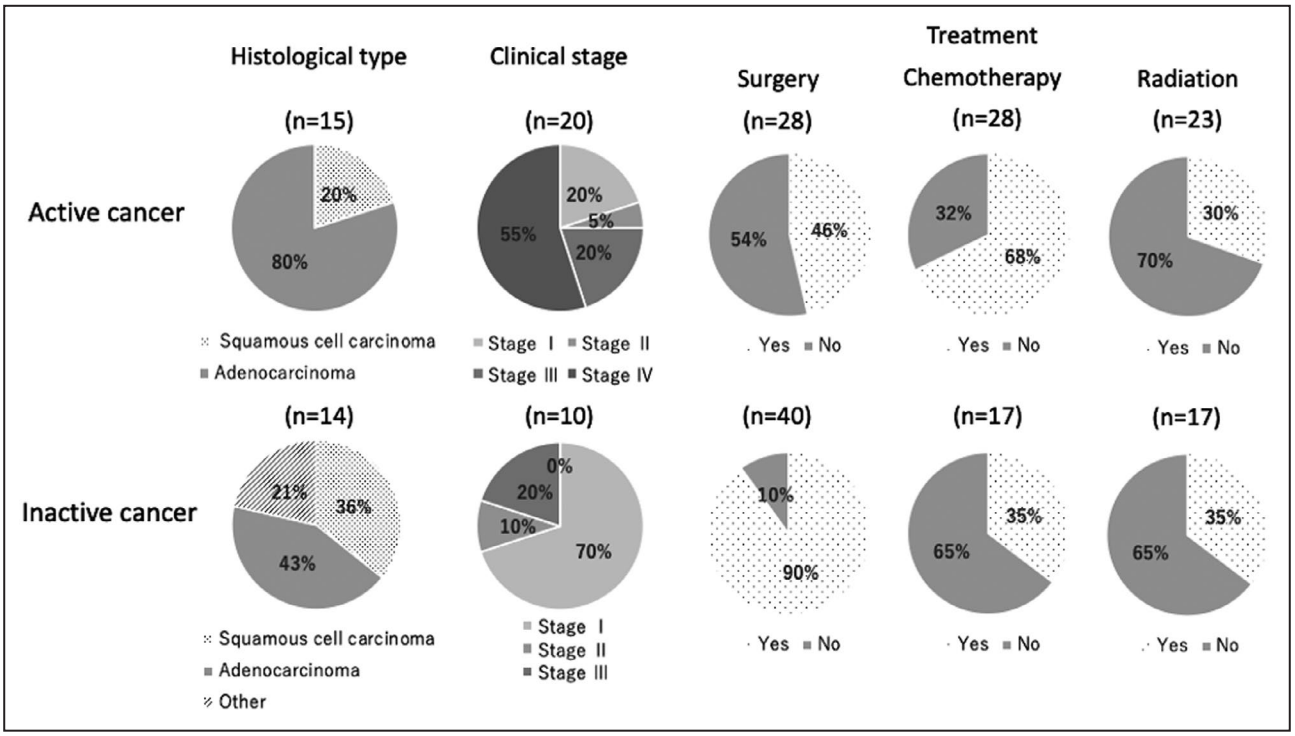

Figure 2. Histological type, clinical stage, and treatment for active and inactive cancers.
The proportions of patients by histological type, clinical stage, and treatment details (surgery, chemotherapy, and radiation) of active and inactive cancers are presented.

Previous studies suggested that ≈4% to 12% of patients with ischemic stroke have comorbid active cancer.[15,20] In particular, the frequency of active cancer in CS was more common, but ranged from 8% to 47%.[15,20,21] Because the present registry enrolled patients with CS who underwent TEE, a semi-invasive and avoidable examination for cancers involving the gastrointestinal tract, those patients in this study were presumed to be small in number. Some studies reported that the ischemic stroke of patients with active cancer presented with multiple infarctions in multiple vascular territories.[4,22] Moreover, this imaging feature was associated with recurrence of stroke,[23] together with elevation of D-dimer levels,[3,4,15] CRP,[24] and several tumor markers of adenocarcinoma.[25] In the present study as well, the presence of infarctions in multiple vascular territories and elevation of CRP were independently associated with active cancer. Although arteriogenic embolism, especially in strokes attributable to emboli from complex aortic plaque, showed multiple infarctions,[26] the present data indicated that infarction in multiple vascular territories was more closely related to active cancer-associated stroke, which was well concordant with the concept of Trousseau syndrome.[9,22,24] D-dimer levels in the present study were not independently associated with active cancer, contrary to previous reports, because the subjects of the present study were limited to patients with CS who had relatively high average D-dimer levels related to a variety of potential embolic mechanisms.

This study had another notable finding, that a history of inactive cancer was significantly related to some atherosclerotic embolic sources, such as contralateral carotid stenosis, ACL in the aortic arch, and aortic valve calcification. It was shown that these pathologic processes coexisted in CS or ESUS,[27,28] and not only ACL in the arch, but aortic valve calcification was regarded as a substantial embolic source of ESUS and CS.[14] As for atherosclerotic burden in cancer, autopsy studies in the 1950s suggested that atherosclerotic changes were rather inconspicuous in patients with cancer.[29,30] Although recent progress in treatment has increased the survival rate of patients with cancer, cardiovascular death has instead increased among them.[12,13] Not only mutual physiological factors, such as chronic inflammation and oxidative stress,[6,31] but recent advances of treatments themselves could accelerate the atherosclerotic burden in patients with cancer.[1,12,13] In particular, chemotherapy induces endothelial dysfunction, thrombophilia, and alteration of mitochondrial metabolism, whereas radiotherapy evokes degeneration and persistent inflammation in vascular endothelium, which last for years and arise over time.[12] Thus, it is possible that atherosclerotic embolic sources in some of the patients with stroke who have inactive cancer are related to past treatment for their malignancy.

Although the follow-up data were limited to the acute stage hospitalization in the present study, recurrence rates of stroke in patients with active cancer and childhood cancer survivors were generally high.[15,32,33] Consequently, it is crucial to elucidate exact embolic sources and pathological features of patients with stroke with active and inactive cancers for the purpose of providing optimal secondary prevention. Antiplatelets are typically used for secondary stroke prevention after stroke attributable to atheroembolism. The optimal treatment for cancer-associated embolic stroke affecting multiple vascular territories is not clear, although previous studies have demonstrated the effectiveness of anticoagulation cancer-associated venous thromboembolism.[19,34,35] Thus, it could be a beneficial implication for medical management to investigate and understand the mechanism of stroke in patients with active and inactive cancer.

There were some limitations to this study. First, this study was retrospective, which might have affected the accuracy of CS diagnosis; the methods to detect covert atrial fibrillation during hospitalization, the protocols for TEE and magnetic resonance imaging, and the interpretation of these findings differed by institute; and there was a lack of standardization. Furthermore, evaluation of intraobserver and interobserver reliabilities was not performed in the current multicenter study. Second, there was a selection bias to perform TEE, a semi-invasive and avoidable examination. In particular, we had no data for the proportion of patients who originally met the criteria of CS but could not undergo TEE in each institution. Third, for the presence and history of cancers, the interpretations of medical records depended on each institution's board, and detailed information of cancer was limited in the present multicenter stroke registry. Regrettably, there was little specific information on the details and periods of chemoradiation therapy for cancers. Last, the follow-up period, limited to the acute stage of hospitalization, was not sufficient to estimate the prognosis of this population with CS. The most important mission of this registry will be to gather longer follow-up data.

CONCLUSIONS

Active and inactive cancers in patients who were originally classified as having CS in the CHALLENGE ESUS/CS registry were not rare, and all patients who underwent TEE had genuinely diverse embolic sources. In the present study, patients with comorbid active cancer had more infarctions in multiple vascular territories, whereas patients with a history of inactive cancer had more atherosclerotic embolic sources potentially causing arteriogenic strokes.

APPENDIX

CHALLENGE ESUS/CS Collaborators

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