Neurology Asia 2023; 28(1) : 99 – 104

Three-territory sign in cancer-related ischemic stroke

[1,2]Zerrin Yildirim *MD*, [1]Tugba Eyigurbuz *MD*, [1]Ece Akalin-Akkas *MD*, [1]Sule Kahraman *MD*, [1]Ebru Nur Karakoprulu *MD*, [1]Mehmet Yerturk *MD*, [1]Selahattin Reyhani *MD*, [1]Nilufer Kale *MD*

[1]Bagcilar Training and Research Hospital, Department of Neurology, Istanbul; [2]Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Neuroscience, Istanbul, Turkey

Abstract

Background & Objective: The presence of multiple acute infarcts in stroke patients indicates cardioembolism in etiology. However, it has also been proposed that 3-territory sign (TTS) with infarction in three different vascular teritories is a radiological marker for cancer. In this study, we aimed to examine TTS in stroke patients with cancer comorbidity as compared to control. *Methods:* Among the patients who were hospitalized with the diagnosis of acute stroke between 2017-2022, 68 patients with a history of cancer were included in this study. Age, sex, medication, vascular risk factors (RF), cancer type, Bamford and TOAST classification, National Institute of Health Stroke Score (NIHSS), modified Rankin Score (mRS) and TTS as imaging findings were recorded. As the control group (CG), 47 stroke patients matched for age, sex, medication and RF were included. *Results:* The most common cancer types were gastrointestinal system, breast and lung, respectively. There was a significant difference between the two groups in terms of Bamford classification and NIHSS. 64.7% of the CaG had infarction in 1 territory, 13.2% in 2 and 13.2% in 3 territories. While 83% of CG had infarction in 1 territory, 14.9% in 2 territories, there were no participants with infarction in 3 territories (p=0.02). After exclusion of the patients with cardioembolic etiology, 14% of CaG had TTS, while no patient had TTS in CG (p=0.047).
Conclusion: Our study supports the finding of TTS in cancer-related stroke, even after excluding cardioembolic etiologies.

Keywords: Three-territory sign, cancer, ischemic stroke

INTRODUCTION

Ischemic cerebrovascular disease occurs in 15% of cancer patients[1], and the 6-month cumulative incidence of ischemic stroke is twice higher in cancer patients compared with control patients.[2] In cancer patients, cerebrovascular disease is the second most common neurological manifestation after metastases.[3]

Although malignancy is known for its association with venous thrombosis, recent studies showed that it is also a significant risk factor for arterial thromboembolism, and 10% of the ischemic stroke patients have comorbid cancer.[4]

Although stroke can occur at any time during malignancy, the risk of ischemic stroke is highest in the first few months (up to 1 year) after cancer diagnosis.[5,6] And also it can be the first manifestation of occult malignancy in 3% of patients and may occur 1-5 months before cancer diagnosis.[7,8] Hypercoagulability, cancer therapy, infections, paraneoplastic disorders, and direct tumour effects are factors involved in the pathogenesis of arterial thrombosis in cancer patients.[6]

Although multiple acute cerebral ischemic infarcts are most frequently attributed to a cardioembolic etiology[9] it is also a feature of cancer associated stroke. The lesions are characterized as small and involving multiple vascular territories[10], indicating proximal embolism caused by cancer-associated hypercoagulation.[6] Since infarction in multiple vascular territories, especially in three vascular territories has been reported in cancer-associated stroke[11,12], Finelli *et al*. developed this finding as a sign called "three-territory sign (TTS)" and suggested it as a radiological marker for cancer-associated stroke.[9,10]

Address correspondence to: Zerrin Yildirim, MD., Bagcilar Training and Research Hospital, Department of Neurology Merkez Mh., Mimar Sinan Caddesi, 6. Sokak, 34100 Bagcilar/Istanbul, Turkey. Tel: +905444746058, email: yildirimzerrin@gmail.com

Date of Submission: 8 January 2023; Date of Acceptance: 26 January 2023

https://doi.org/10.54029/2023mjf

Following that, Nouh *et al*. compared cancer patients with acute stroke and no atrial fibrillation, with the patients with known atrial fibrillation (AF) and without cancer by using TTS. They showed that the frequency of TTS is 6-times higher in cancer patients than in stroke patients with AF.[9]

In this study, we aim to evaluate TTS in stroke patients with a history of cancer compared with stroke patients without cancer. Our hypothesis is that stroke patients with a history of cancer would show higher TTS than the control group, even when we exclude those with cardioembolic etiology.

METHODS

Participants

This study was carried out according to a protocol approved by the Ethics Committee of the Bagcilar Training and Research Hospital and all participants provided written informed consent.

The records of patients who were hospitalized in the Neurology Clinic of Bagcilar Training and Research Hospital between January 2017 and January 2022 were retrospectively reviewed, and 68 patients with a history of cancer were included as the cancer group (CaG). As the control group (CG), 47 stroke patients matched for age, sex, medication and vascular risk factors (RF) were included. Age, sex, medication, RF, type of cancer, Bamford and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores at entry and discharge, clinical course (same, better and worse), hemorrhagic transformation, systemic complications (pneumonia, urinary tract infections, deep vein thrombosis, pulmonary embolism, bleeding and others), outcome (home discharge, transfer to another clinic, transfer to intensive care unit), and three-territory sign as neuroimaging findings were collected and recorded.

All the patients had at least one cranial magnetic resonance imaging (MRI), computerized tomography or MRI angiography, and cardiac investigations (electrocardiography, transthoracic echocardiogram) to define stroke etiology. If we did not detect any cardioembolic source in electrocardiography and transthoracic echocardiogram, we depended on 24-hour holter monitoring, transesophageal echocardiography and digital subtraction angiography performed in some patients.

Stroke types were classified as ischemic stroke, transient ischemic attack, and hematoma. Ischemic strokes were further classified into four main groups including total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), posterior circulation infarction (POCI), and lacunar infarction (LACI) according to the Bamford Clinical Classification.

Etiological subtypes were classified as large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology according to the TOAST classification.

Hypertension, diabetes mellitus, AF, coronary artery disease, heart failure, previous stroke, smoking, obesity, and dyslipidemia were the RFs for stroke.

Diffusion-weighted MRI (DWI) patterns of the patients were classified as 1, 2, or 3 territories[9,10] as follows; *One Territory:* Unilateral, single, or multiple acute ischemic strokes involving the anterior or the posterior circulation; *Two Territory:* Unilateral, single, or multiple acute ischemic strokes involving bilateral anterior circulation or the anterior circulation plus posterior circulation; *Three Territory:* Bilateral, single, or multiple acute ischemic strokes involving the bilateral anterior and posterior circulation.

Statistical analysis

Statistical analysis was performed using SPSS version 28.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean, standard deviation, median, minimum, maximum, frequency, and percentage. In comparing demographic and clinical data, the Kruskal-Wallis test was used. The Pearson chi-square and Fischer's exact tests were used to compare the frequencies and percentages.

RESULTS

Cancer types are showed in Table 1. Comparison of the demographic and clinical variables of CaG and CG are shown in Table 2. There were no significant differences among the groups in terms of age ($p = 0.064$), sex ($p = 0.85$), medication ($p = 0.055$), RFs ($p = 0.059$), TOAST classification ($p = 0.18$), mRS scores at entry and discharge ($p = 0.065$ and $p = 0.128$, respectively), hemorrhagic transformation ($p = 1.0$), and outcome ($p = 0.13$).

Although there was no statistically significant difference between the two groups in terms of TOAST classification, CaG patients had higher rate of undetermined stroke etiology than the CG;

Table 1: Cancer types

Type of cancer	*n (%)*
GIS	18 (26.5)
Breast	11 (16.2)
Lung	10 (14.7)
Urinary tract	8 (11.8)
Hematological	4 (5.9)
Nasopharynx, larynx	4 (5.9)
Connective tissue, bone	4 (5.9)
Skin	3 (4.4)
Brain	2 (2.9)
Endometrium	2 (2.9)
Testicle	1 (1.5)
Thyroid	1 (1.5)

GIS: Gastrointestinal system

42.6% of the CaG patients (n= 29) and 29.8% of the CG patients (n = 14) had undetermined stroke etiology; 27.9% of the CaG patients (n = 19) had cardioembolic etiology, all of which was atrial fibrillation; 13.2% of the CaG (n = 9) had small vessel occlusion and 7.4% (n = 5) had large-artery atherosclerosis.

Bamford classification (p = 0.009) was significantly different between the two groups. While PACI and POCI were dominant in CaG, PACI, LACI, and POCI were dominant in CG. NIHSS scores of CaG at entry and discharge were significantly higher than the CG (p = 0.031 and p = 0.03, respectively). Clinical course was significantly different between the two groups (p <0.001). While participants with same and better clinical course were dominant in both groups, the percentage of worse patients was higher in CaG than in CG. Systemic complications were significantly different between the two groups (p = 0.013). Pneumonia, urinary tract infections, deep vein thrombosis, and pulmonary embolism were more frequent in the CaG than the CG.

When the neuroimaging findings were classiffied as territory signs in ischemic stroke patients (1, 2, and 3) and hematoma, the two groups were significantly different (p = 0.022). The proportion of participants with three-territory sign or hematoma in CaG were higher than in the CG (Table 3).

To evaluate the TTS in patients other than strokes with cardioembolic etiology we excluded patients with hematoma and stroke with cardioembolic etiology. In the comparison made after this exclusion, CaG had significantly higher territory sign than the CG in Kruskal-Wallis test (p = 0.022). Pearson chi-square test also showed a significant difference between the two groups (p = 0.047). While 90.6% of CG (n = 29) had 1 territory infarction, 9.4% (n = 3) had 2 territory infarction and none of CG had three territory infarction. While 69.8% of CaG (n = 30) had 1 territory infarction, 16.3% (n = 7) had 2 territory infarction and 14% (n = 6) had three-territory infarction (Table 4).

DISCUSSION

This study aimed to investigate TTS in stroke patients with a history of cancer. Our main expectation was that the stroke patients with a history of cancer would show higher TTS than the control group. Our CaG patients showed higher TTS frequency than the CG, even after excluding the patients with cardioembolic etiology.

TTS was first suggested as a neuroimaging marker in cancer-associated stroke by Finelli *et al*.[10] The authors retrospectively evaluated the stroke patients with DWI lesions involving 3 or more vascular territories in the absence of an identifiable embolic source. They reported that the most frequent etiology was cancer-related infarctions (22%). Following that Nouh *et al*. compared stroke patients with a known malignancy and stroke patients with AF.[9] The authors showed that TTS was observed in 23.4% of the patients with malignancy, but only 3.5% of the patients with AF.

In their later work, Finelli evaluated MRI findings of stroke patients retrospectively. Of the 2792 stroke patients, 22 had TTS. 16 of 22 patients with TTS had cancer in etiology.[13] The authors reported that malignancy was known only in 7 patients at stroke presentation. The malignancy was occult in 9 patients. Cancer types were cholangiocarcinoma, adenocarcinoma of lung, pancreatic carcinoma, non-small cell carcinoma of lung, adenocarcinoma of breast, origin unknown adenocarcinoma, carcinoid, ovarian carcinoma, and unknown lung mass. Adenocarcinomas were reported as the most common type in cancer-related stroke.[6,14-16]

GIS cancers were the most common type of cancer with a rate of 26.5%, in our study. It was followed by breast, and lung cancers. We could not report subtypes of cancer, since we did not collect the histological diagnoses data. Yesilot *et al*., has reported that the most common cancer type in stroke patients was gastrointestinal tract and hepatobiliary systems.[17] In another study. lung cancer was reported as the most common cancer

Table 2: Demographic and clinical findings according to the diagnostic groups

	Cancer Group (n=68)	Control Group (n= 47)	p
Age, *mean ± Sd.*	67.8 ± 11.2	63.2 ± 12.5	0.064[†]
Sex, F:M, *n (%)*	29:39 (42.6:57.4)	19:28 (40.4:59.6)	0.85[‡]
Medication, *n (%)*			
None	26 (38.2)	18 (38.3)	0.055[§]
Antiaggregants	11 (16.2)	18 (38.3)	
Anticoagulants	7 (10.3)	2 (4.3)	
Antiaggregants and Anticoagulants	2 (2.9)	1 (2.1)	
Other	22 (32.4)	8 (17)	
Risk factors, *n (%)*			0.059[§]
1 RF	19 (27.9)	7 (14.9)	
2 RF	8 (11.8)	11 (23.4)	
≥3 RF	14 (20.6)	16 (34)	
No RF	27 (39.7)	13 (27.7)	
Bamford Classification, *n (%)*			
TACI	4 (5.9)	1 (2.1)	0.009[§*]
PACI	36 (52.9)	18 (38.3)	
POCI	16 (23.5)	11 (23.4)	
LACI	6 (8.8)	16 (34)	
Hematoma	6 (8.8)	1 (2.1)	
TOAST Classification, *n (%)*			
Large-artery atherosclerosis	5 (7.4)	8 (17)	0.18[§]
Cardioembolism	19 (27.9)	14 (29.8)	
Small-vessel occlusion	9 (13.2)	9 (19.1)	
Other	0	1 (2.1)	
Undetermined etiology	29 (42.6)	14 (29.8)	
Entry NIHSS, *mean ± Sd.*	4.5 ± 3.8	3.4 ± 3.4	0.031[†*]
Discharge NIHSS, *mean ± Sd.*	4.2 ± 3.7	2.4 ± 2.5	0.03[†*]
Entry mRS, *mean ± Sd.*	0.5 ± 1.2	0.9 ± 1.5	0.065[†]
Discharge mRS, *mean ± Sd.*	1.9 ± 1.8	1.4 ± 1.8	0.128[†]
Clinical course, *n (%)*			
Same	45 (66.2)	17 (36.2)	<0.001[§*]
Better	15 (22.1)	29 (61.7)	
Worse	8 (11.8)	1 (2.1)	
Systemic complications, *n (%)*			
None	42 (61.8)	42 (89.4)	0.013[§*]
Pneumonia, urinary tract infections	17 (25)	4 (8.5)	
DVT, pulmonary embolism	2 (2.9)	0	
Bleeding	6 (8.8)	0	
Other	1 (1.5)	1 (2.1)	
Hemorrhagic transformation, *n (%)*	2 (2.7)	1 (2.1)	1.0[‡]
Outcome, *n (%)*			
Home discharge	57 (83.8)	45 (95.7)	0.13[§]
Transfer to another clinic	3 (4.4)	1 (2.1)	
Transfer to intensive care unit	8 (11.8)	1 (2.1)	

n: number; Sd: standard deviation; F: female; M: male; RF: risk factors, TACI: total anterior circulation infarction; PACI: partial anterior circulation infarction; POCI: posterior circulation infarction; LACI: lacunar infarction; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; DVT: deep vein thrombosis

[*]$p<0.05$

[†]Kruskal-Wallis test

[‡]Fisher's Exact test

[§]Pearson chi-square test

Table 3: Neuroimaging findings according to the diagnostic groups.

	CaG (n=68)	CG (n= 47)	p
Neuroimaging findings, *n (%)*			
1 territory infarction	44 (64.7)	39 (83)	0.022‡*
2 territory infarction	9 (13.2)	7 (14.9)	
3 territory infarction	9 (13.2)	0	
Hematoma	6 (8.8)	1 (2.1)	

n: number
*p<0.05
‡Pearson chi-square test

type in malignancy related stroke patients.[18] On the other hand, TTS was reported in 44.12% of the patients with malignant gastrointestinal tumor.[19] In our study 22.2% of the stroke patients with GIS cancer had TTS, but without any cardioembolic etiology. GIS cancers were the most common cancer type with a rate of 66.6% in 6 patients, who had TTS and did not have any cardioembolic source.

Cancer related acute ischemic stroke is associated with early neurological deterioration, higher recurrence rates, poor prognosis, and higher mortality rates[17,20-22], with TTS reported as an independent risk factor for prognosis.[19] As in other studies cancer patients showed worse neurological status as measured via NIHSS, worse clinical course and more systemic complications in our study.

Our data replicates Finelli's findings of TTS in cancer patients without any cardioembolic source in a design with a control group, which includes stroke patients matched for age, sex, medication and risk factors. Our findings showed that undetermined etiology in TOAST classification and TTS are more frequent in the stroke patients with a history of cancer. These findings indicate that clinicians should suspect a cancer when they could not determine the etiology in the stroke patients who had TTS.

The major limitation of this study is its retrospective and single-center design, which limits the information reported. We could not collect all needed data such as DIC parameters, histological diagnosis, grade of cancer. Our study also did not include patients who had thrombolytic treatment or thrombectomy because our center does not have an acute stroke unit, and we can not perform acute treatment of patients with thrombolysis and thrombectomy. Such patients are referred to appropriate centers by the emergency call center.

DISCLOSURE

Financial support: None

Conflicts of interest: None

Table 4: Territory sign according to the diagnostic groups after excluding patients with hematoma and patients had strokes with cardioembolic etiology

	Cancer Group (n=43)	Control Group (n= 32)	p
Territory sign, *mean ± Sd.*	1.44 ± 0.73	1.09 ± 0.296	0.022†*
Territory sign, *n (%)*			
1	30 (69.8)	29 (90.6)	0.047‡
2	7 (16.3)	3 (9.4)	
3	6 (14)	0	

n: number; Sd: standard deviation
*p<0.05
†Kruskal-Wallis test
‡Pearson chi-square test

REFERENCES

1. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. *Medicine* (Baltimore) 1985;64:16-35. https://doi.org/10.1097/00005792-198501000-00002
2. Navi BB, Reiner AS, Kamel H, *et al*. Risk of arterial thromboembolism in patients with Cancer. *J Am Coll Cardiol* 2017;70:926-38. https://doi.org/10.1016/j.jacc.2017.06.047
3. Zhang YY, Chan DKY, Cordato D, Shen Q, Sheng AZ. Stroke risk factor, pattern and outcome in patients with cancer. *Acta Neurol Scand* 2006;114(6):378-83. https://doi.org/10.1111/j.1600-0404.2006.00709.x
4. Navi BB, Iadecola C. Ischemic stroke in cancer patients: A review of an underappreciated pathology. *Ann Neurol* 2018;83(5):873-83. https://doi.org/10.1002/ana.25227
5. Bang OY, Chung JW, Lee MJ, *et al*. Cancer-related stroke: An emerging subtype of ischemic stroke with unique pathomechanisms. *J Stroke* 2020;22(1):1-10. https://doi.org/10.5853/jos.2019.02278
6. Salazar-Camelo RA, Moreno-Vargas EA, Cardona AF, Bayona-Ortiz HF. Ischemic stroke: A paradoxical manifestation of cancer. *Crit Rev Oncol Hematol* 2021;157:103181. https://doi.org/10.1016/j.critrevonc.2020.103181
7. Uemura J, Kimura K, Sibazaki K, Inoue T, Iguchi Y, Yamashita S. Acute stroke patients have occult malignancy more often than expected. *Eur Neurol* 2010;64(3):140-4. https://doi.org/10.1159/000316764
8. Navi BB, Reiner AS, Kamel H, *et al.* Arterial thromboembolic events preceding the diagnosis of cancer in older persons. *Blood* 2019;133:781-9. https://doi.org/10.1182/blood-2018-06-860874
9. Nouh AM, Staff I, Finelli PF. Three territory sign: An MRI marker of malignancy-related ischemic stroke (Trousseau syndrome). *Neurol Clin Pract* 2019;9(2):124-8. https://doi.org/10.1212/CPJ.0000000000000603
10. Finelli PF, Nouh A. Three-territory DWI acute infarcts: diagnostic value in cancer associated hypercoagulation stroke (Trousseau syndrome). *Am J Neuroradiology* 2016;37:2033-6. https://doi.org/10.3174/ajnr.A4846
11. Kwon HM, Kang BS, Yoon BW. Stroke as the first manifestation of concealed cancer. *J Neurol Sci* 2007;258:80-3. https://doi.org/10.1016/j.jns.2007.02.035
12. Kim SJ, Park JH, Lee MJ, *et al*. Clues to occult cancer in patients with ischemic stroke. *PLoS One* 2012;7:e44959. https://doi.org/10.1371/journal.pone.0044959
13. Finelli PF. MR three-territory sign in cancer-associated hypercoagulation stroke (Trousseau Syndrome): An overlooked diagnostic feature: MR three-territory sign. *Neurologist* 2021;27(2):37-40. https://doi.org/10.1097/NRL.0000000000000356
14. Dearborn JL, Urrutia VC, Zeiler SR. Stroke and cancer- A complicated relationship. *J Neurol Transl Neurosci* 2014;2(1):1039.
15. Quintas S, Rogado J, Gull´on P, et al. Predictors of unknown cancer in patients with ischemic stroke. *J Neurooncol* 2018;137(3):551-7. https://doi.org/10.1007/s11060-017-2741-0
16. Alvarez-Perez FJ, Verde I, Us´on-Martín M, Figuerola-Roig A, Ballabriga-Planas J, Espino-Iba˜nez A. Frequency and mechanism of ischemic stroke associated with malignancy: a retrospective series. *Eur Neurol* 2012;68(4):209-13. https://doi.org/10.1159/000341343
17. Yesilot N, Ekizoglu E, Coban O. Clinical features of cancer associated ischemic stroke. *Noropsikiyatri Arsivi* 2018;55(2):113-7. https://doi.org/10.29399/npa.22999
18. Cestari DM, Weine DM, Panageas KS, Segal AZ, DeAngelis LM. Stroke in patients with cancer: incidence and etiology. *Neurology* 2004;62(11):2025-30. https://doi.org/10.1212/01.wnl.0000129912.56486.2b.
19. Liu Y, Li X, Song F, *et al*. Clinical features and prognostic factors of acute ischemic stroke related to malignant gastrointestinal tumor. *Front Neurol* 2021;12:777483. https://doi.org/10.3389/fneur.2021.777483
20. Kneihsl M, Enzinger C, Wünsch G, *et al*. Poor short-term outcome in patients with ischaemic stroke and active cancer. *J Neurol* 2016;263:150-6. https://doi.org/10.1007/s00415-015-7954-6
21. Zhang YY, Cordato D, Shen Q, Sheng AZ, Hung WT, Chan DK. Risk factor, pattern, etiology and outcome in ischemic stroke patients with cancer: a nested case-control study. *Cerebrovasc Dis* 2007;23:181-7. https://doi.org/10.1159/000097639
22. Nam KW, Kim CK, Kim TJ, *et al.* D-dimer as a predictor of early neurologic deterioration in cryptogenic stroke with active cancer. *Eur J Neurol* 2017;24:205-11. https://doi.org/10.1111/ene.13184