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Clinical Features of Cancer Associated Ischemic Stroke

Kanserle İlişkili İskemik İnmenin Klinik Özellikleri

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ABSTRACT

Introduction: Cerebrovascular disease is the second most common cause of central nervous system involvement in cancer patients after metastases. Procoagulant substances secreted by tumour cells, cancer therapy, and embolus from tumour have been implicated in ischemic stroke (IS) in cancer patients.

Methods: Four thousand twenty patients with IS were prospectively recorded to the Istanbul Medical School Stroke Registry from August 1997 to May 2016. Ninety-two patients with IS and cancer and 3928 IS patients without cancer constituted the two groups.

Results: Hypertension, hyperlipidemia, and congestive heart failure were less commonly encountered in cancer stroke patients. Lacunar and posterior circulation syndromes were less common and total anterior circulation syndrome was more common in cancer patients (p<0.001). Multiple territory infarcts were more frequently seen in patients having overt or non-overt disseminated intravascular coagulopathy (DIC) compared to those without DIC. Median survival was significantly shorter in patients with cancer-related stroke.

Conclusion: Cancer associated stroke without other underlying etiology is a specific group of stroke patients presenting with multiple territorial infarcts, overt or non-overt disseminated intravascular coagulopathy, and poor prognosis.

Keywords: Cancer, ischemic stroke

ÖZ

Amaç: Serebrovasküler hastalık, kanser hastalarında metastazlardan sonra ikinci en sık merkezi sinir sitemi tutulumudur. Kanserli iskemik inme hastalarında, tümör hücrelerinden salınan prokoagülan maddeler, kanser tedavisi ve tümör embolisi gibi mekanizmalarla inme geliştiği düşünülmektedir.

Yöntem: İskemik inmeli 4020 hasta Ağustos 1997 – Mayıs 2016 arasında İstanbul Tıp Fakültesi İnme Veri Bankası'na prospektif olarak kaydedilmiştir. Çalışmada incelenen iki grubu, kanseri olan 92 ve olmayan 3928 iskemik inmeli hasta oluşturmuştur.

Bulgular: Kanserli iskemik inme hastalarında, hipertansiyon, hiperlipidemi ve konjestif kalp yetersizliği daha az saptanmıştır. Kanserli hastalarda, laküner ve arka sistem sendromu inmeleri daha az, total anterior sirkülasyon sendromu daha fazla görülmüştür (p<0,001). Multipl teritoryel infarktlar, açık veya açık olmayan dissemine intravasküler koagülopatisi (DİK) olan kanser hastalarında olmayanlara göre daha çok saptanmıştır. Kanserle ilişkili inmeli hastalarda medyan sağkalım anlamlı olarak daha kısa bulunmuştur.

Sonuç: Başka etyolojik neden olmayan kanserli inmeli hastalar, multipl teritoryal infarktlar, açık veya açık olmayan DİK ile kendini gösteren ve kötü prognozlu özgün bir inme grubu oluşturmaktadır.

Anahtar Kelimeler: Kanser, iskemik inme

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INTRODUCTION

Cerebrovascular disease is one of the most common central nervous system involvement in cancer patients after metastases (1). Procoagulant substances secreted by tumour cells, cancer therapy, and embolus from tumour have been implicated in ischemic stroke (IS) in cancer patients (2). Malignancy and stroke are both accepted as major causes of morbidity and mortality (3). Moreover, the thrombotic diathesis begins before the evidence of cancer in some patients.

Understanding the clinical associations between stroke and cancer seems to be important for determining their causal relationship, and for planning further investigations and therapy. Furthermore, there is limited data for the necessity of screening cancer in ischemic stroke patients. In this study, we aimed to evaluate the clinical features of patients with a history of cancer or who were diagnosed as having cancer at the time of IS, and also to compare their clinical characteristics to those of non-cancer IS patients

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registered in the Istanbul Medical School Stroke Registry (IMSSR) (4). We also hypothesized that cancer related stroke long-term survival would be different from those who had other conventional stroke mechanisms, and collected long-term outcome data of patients who had an IS and cancer.

METHODS

Four thousand twenty patients with IS were prospectively recorded to the IMSSR from August 1997 to May 2016. Ninety-two patients with IS and cancer, and 3928 IS patients without cancer constituted the two groups (4). Consent was waived since the study did not involve any procedures or interventions that were study related. All the patients had at least one cranial CT or MRI, vascular, and cardiac investigations to define stroke etiology. One hundred and twenty-three variables including; age, sex, risk factors, time to admission, level of consciousness, severity of neurologic deficits as reflected by inability to lift the symptomatic arm or inability to walk, early deterioration (worsening of stroke symptoms within 2 days), blood pressure at entry, modified Rankin score (mRS) at entry and discharge, clinical subtypes according to the "Oxfordshire Community Stroke Project" (OCSP) classification, etiological subtypes according to the "Trial of Org 10172 in Acute Stroke Treatment" (TOAST) classification, infarct localization, in hospital recurrent stroke, neurological (edema and hemorrhagic transformation) and systemic complications (cardiovascular complications, pneumonia, other infections, deep vein thrombosis, pulmonary embolism), length of hospital stay, and death were recorded for all patients (5, 6). Disseminated intravascular coagulopathy (DIC) was evaluated with d-dimer, fibrinogen, and fibrin degradation product (FDP) levels whenever possible in the cancer group (7).

We classified the relation between cancer and the pathogenesis of stroke as follows: 1) cancer-related stroke, indicating active cancer without any other apparent cause for stroke; 2) cryptogenic stroke with a history of cancer, that is, cancer in history but no macroscopic cancer was detectable at the time of stroke onset; 3) cryptogenic stroke with later diagnosed cancer; 4) other etiology with a history of cancer, that is, the individual had cancer in history, but there was no detectable cancer at the time of stroke onset, and there was another apparent cause for stroke; and 5) other etiology with later diagnosed cancer.

Categorical variables between the two groups were compared using Chi-square test or Fisher's exact test, and non-parametric variables were compared using Mann-Whitney U test with SPSS version 11.0 (IBM, USA). Wilcoxon Signed Ranks Test was used for in-group analyses, and cumulative mortality in the cancer group was analyzed with the Kaplan-Meier life table method using the log-rank test.

RESULTS

Our study groups constituted of 92 IS patients with cancer and 3928 IS patients without cancer and there were not any significant differences in age and gender distribution between the two groups. The demographic and clinical characteristics and ischemic risk factors of the cancer and non-cancer groups are given in Table 1. Hypertension, hyperlipidemia and congestive heart failure were less commonly encountered in cancer stroke patients. Lacunar and posterior circulation syndromes were less common and total anterior circulation syndrome was more common in cancer patients (p<0.001) (Figure 1). Neuroimaging studies showed more frequently infarcts in multiple arterial territories in the cancer group (p=0.003) (Figure 2). Among patients having cancer, the rate of hemorrhagic transformation and systemic complications were also more frequent. Furthermore, recurrent stroke during hospital stay and in-hospital mortality rate were higher in cancer patients without reaching statistical significance (Table 1).

Ischemic stroke patients diagnosed with cancer had 18 different tumour types, most commonly in gastrointestinal tract and hepatobiliary systems [31/92 (33.6%)], followed by lung cancer [24/92 (26%)] (Table 2). Eleven patients (11.9%) were diagnosed as having cancer during their acute hospital stay for stroke. Fifteen patients (16.3%) had a stroke within

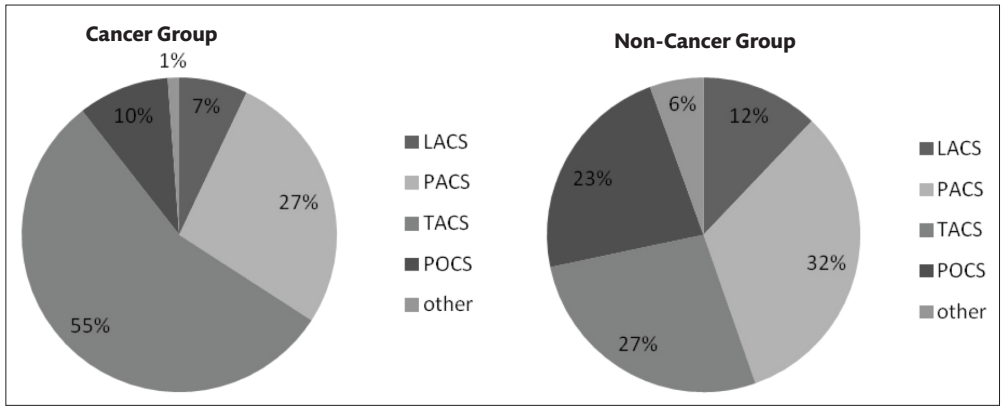


Figure 1. The distribution of the stroke syndromes in ischemic stroke patients with and without cancer.

LACS: lacunar syndrome, POCS: posterior circulation syndrome, PACS: partial anterior circulation syndrome, TACS: total anterior circulation syndrome.

Lacunar and posterior circulation syndromes are less common and total anterior circulation syndrome is more common in cancer patients than in non-cancer patients (p<0.001).

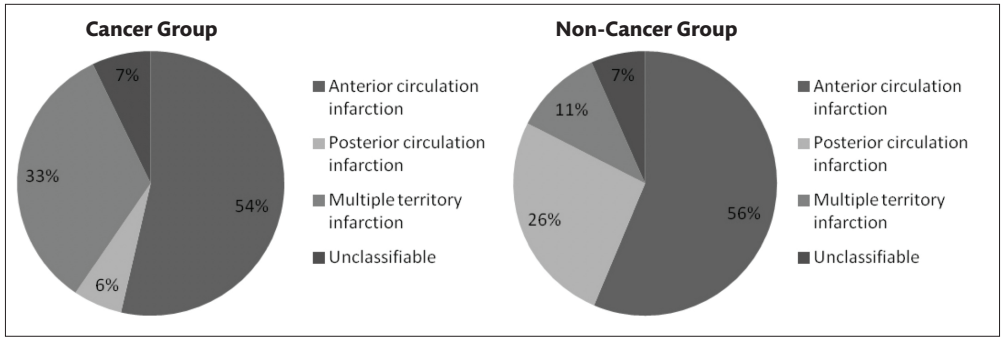


Figure 2. The distribution of the infarct localizations in ischemic stroke patients with and without cancer.

Infarcts in multiple arterial territories are seen more frequently in the cancer group than in non-cancer group (p=0.003).

Table 1. Demographic and clinical features of the patients having ischemic stroke with and without cancer

	Cancer IS patients n (%) or (mean ± SD)	Total number of Cancer IS patients (n)*	Non-cancer IS patients n (%) or (mean ± SD)	Total Non-cancer IS patients (n)*	P
Gender (m/f)	55/37	92	2115/1813	3928	NS
Age	64.55±12.47	92	64.64±15.26	3851	NS
History of:					
Congestive heart failure	4 (5.3)	75	281 (15.5)	1807	0.013***
Coronary artery disease	14 (16.5)	85	814 (23.9)	3721	NS
Peripheral artery disease	5 (5.7)	88	223 (5.9)	3791	NS
Hypertension	36 (46.1)	78	2661 (72.2)	3683	<0.001**
Hyperlipidemia	18 (22.5)	80	1508 (43.3)	3566	<0.001**
Diabetes	23 (25.5)	90	1019 (26.9)	3783	NS
Metabolic syndrome	3 (6.8)	44	69 (7.5)	918	NS
Smoking	32 (40)	80	1424 (37.3)	3812	NS
Alcohol consumption	9 (10.3)	87	470 (12.1)	3876	NS
Migraine	2 (4.2)	47	21 (2.2)	938	NS
Oral contraceptive use	0 (0)	44	40 (4.6)	874	NS
Sleep disorders	2 (4.4)	45	40 (4.3)	928	NS
TIA	8 (9.1)	88	488 (12.9)	3793	NS
Admission with the first stroke	76 (82.6)	92	2903 (75.6)	3841	NS
TIA preceding stroke	3 (6.5)	46	248 (7.2)	3431	NS
Maximum deficit with stroke	54 (60)	90	2352 (65)	3622	NS
Systolic blood pressure at entry	138±25	49	148±29	2783	0.023***
Diastolic blood pressure at entry	87±22	49	86±17	2783	0.281
Seizure accompanying stroke	0 (0)	45	25 (2.7)	923	NS
Headache with stroke	27 (30.3)	89	668 (18.2)	3661	0.004**
Multiple acute infarcts	23 (25)	92	145 (3.7)	3929	<0.001**
Asymptomatic infarcts	15 (27.3)	55	607 (18.8)	3229	NS
Lesions of asymptomatic vessels	7 (15.5)	45	514 (17.2)	2991	NS
Recurrent stroke	3 (6.5)	46	134 (4)	3315	NS
Hemorrhagic transformation	12 (23.5)	51	309 (9.9)	3129	0.003**
Edema	3 (3.5)	85	345 (10.3)	3331	0.043****
Systemic complication	53 (73.6)	72	1180 (33.2)	3549	<0.001**
In-hospital death	10 (10.9)	92	331 (8.4)	3923	0.5
NIHSS on admission	8.5±6.6	86	9.8±6.9	954	NS
Clinical course in the first 48 hours Same Better Worse	 58 (67.4) 8 (9.3) 20 (23.2)	86	 1822 (19) 824 (22.2) 1069 (28.8)	3715	0.001**
The changes in mRS (Between the mRS scores of entry and discharge)*****	0.08±1.062	90	0.49±1.062	3772	<0.001

*Total number of patients having available data
** Significant with Chi-square test
*** Significant with Mann-Whitney U test
****Significant with Fisher's exact test
*****The mRS scores at entry and discharge did not show any significant difference in IS patients with cancer (p=0.4, Wilcoxon Signed Ranks Test). But mRS scores in IS patients without cancer were significantly lower at discharge (p<0.01, Wilcoxon Signed Ranks Test).
mRS, Modified Rankin Scale; NS, Not significant.

1 year after their cancer diagnosis. The rest of the patients had been diagnosed as having cancer for more than 1 year prior to stroke onset or the temporal relationship between stroke and cancer was unknown. Twenty-five cancer patients had other pathogenesis for stroke, whereas 57 patients suffered a cancer-related stroke (Table 2).

Disseminated intravascular coagulopathy was evaluated in cancer patients whenever possible, and especially in those with adenocancer types which are known to be associated with hypercoagulability and DIC (8). D-dimer was evaluated in 20 patients, it was normal in 1 patient, elevated in the rest, and >500ug/L in 16 patients (mean: 3275 µg/L ±3028). Fibrinogen was evaluated in 16 patients (mean: 478 mg/dl ±184), FDP levels were evaluated in 7 patients, 6 patients had >20 µg/ml and 1 patient had <5 µg/ml. Overt DIC was diagnosed in 8 patients. We could not find an association between the presence of adenocancer with overt or non-overt DIC, but multiple territory infarcts were more frequently seen in patients having overt or non-overt DIC compared to those without DIC (9 of 18 versus 14 of 51 patients, p not significant). Similarly, MRI showed a higher rate of multiple acute ischemic lesions in patients with cancer related stroke in comparison to the patients with other etiology, but this difference did not reach statistical significance (18 of 43 versus 5 of 26 patients)

In-group analyses of the cancer patients showed that 6 of 57 cancer-related stroke patients versus 3 of the 35 remaining patients died during hospital stay (p not significant). However, median survival was significantly

Table 2. Cancer type and its relationship with stroke

Cancer characteristics	N: 92 (%)
Primary cancer location:	
Brain/CNS	1 (1.1)
Breast	4 (4.3)
Gastrointestinal tract, hepatobiliary, liver	31 (33.6)
Head and neck cancer	2 (2.2)
Lungs/respiratory tract	24 (26)
Lymphoma	4 (4.3)
Prostate/urinary tract	1 (1.1)
Melanoma	10 (10.1)
Other	15 (16)
Etiology and cancer:	
Cancer-related stroke	57 (61.9)
Cryptogenic stroke with history of cancer	7 (7.6)
Cryptogenic stroke with later-diagnosed cancer	3 (3.3)
Other etiology with history of cancer	21 (22.8)
Other etiology with later-diagnosed cancer	4 (4.3)
Time of malignancy	
Pre-stroke	76 (82.6)
Post-stroke	16 (17.4)

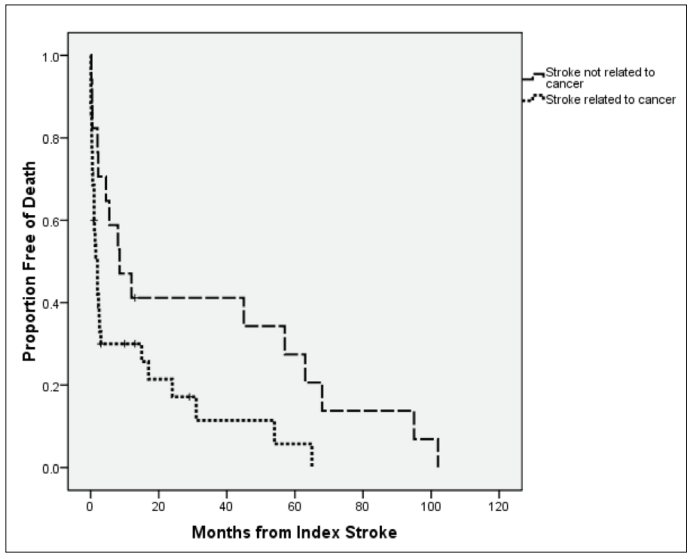


Figure 3. Kaplan-Meier plot of survival free of death of the cancer patients having stroke related and not related to cancer.

shorter in patients with cancer-related stroke (2 months; IQR, 1–3) than the rest of the patients having cancer (8.5 months; IQR, 0–17.2; log-rank test; p=0.021) (Figure 3).

DISCUSSION

A subset of patients with cancer and IS who do not have conventional stroke etiology has been classified as cryptogenic stroke in earlier reports. Pancreatic, gastric, lung and respiratory tract cancer are diagnosed most commonly in stroke patients (3, 9), similar to our findings. Although some studies did not find any significant difference between patients with and without cancer in terms of traditional vascular risk factors (3, 10), hypertension, hyperlipidemia were less frequent, and systolic blood pressure at entry was lower in our cancer group.

Other cohorts with cancer and IS usually had elevated D-dimer levels (8, 10, 11), and our cohort showed a similar profile although D-dimer investigation was done in only 11% of the cohort. Cancer associated thrombosis is one of the complications of DIC occurring in the course of malignancy (9), especially in the patients having adenocancer. In this study, we could not find an association between the presence of adenocancer with overt or non-overt DIC which may be related to the small cohort size. Furthermore, CS patients without conventional stroke mechanisms had multiple territorial infarcts, and/or bihemispheric or anterior and posterior involvement in various studies (10–13) which was also the case in our cohort. Our findings show that multiple territory infarcts were more frequently seen in patients diagnosed with non-overt or overt DIC.

In the presented cohort, cancer patients suffered more frequently from hemorrhagic transformation, and had worse clinical outcome during hospitalization as reflected by the changes in MRS scores than their stroke non-cancer counterparts. This finding has been reported in other cancer associated IS cohorts (14, 15). Similarly, shorter survival has also been shown in other cohorts where the stroke mechanism was hypercoagulability due to cancer (3, 13, 15, 16). These three features reported in the literature points to a discrete group of cancer patients where stroke mechanism was classified as cryptogenic which essentially indicates a hypercoagulability caused by cancer. These groups of patients usually have advanced metastatic adenocarcinomas causing non-overt DIC, and consequently IS stroke involving multiple arterial territories with poor prognosis. Identification of such a pattern may also help discover a concealed cancer presenting with IS compatible with this phenotype. Our findings closely resemble those from Korea, North America, and Australia suggesting a uniform phenotype of cancer associated IS across different geographical regions, which may indicate a unique underlying pathological mechanism in this specific group of patients.

Limitations of our study are; limited availability of DIC parameters, 39% unknown long-term status, single center experience, lack of post-stroke follow-up data in the non-cancer group, and retrospective design. However, spanning over 19 years of consecutive patients' data in an experienced stroke center reflecting clinical practice without referral bias may be considered as the strength of our data.

In this study investigating clinical and radiological findings as well as long-term survival in the cancer patients, our findings show that this subset of patients have a distinctive phenotype necessitating a unique management approach. We conclude that IS patients with cancer as the underlying etiology deserve special attention for stroke evaluation, and IS patients without known cancer but with multiple territorial infarcts and/or with DIC should be screened for cancer.

This study was first presented at the 6th World Stroke Congress (24-27 September 2008, Vienna).

Bu çalışma, ilk olarak 6. Dünya İnme Kongresi'nde (24-27 Eylül 2008, Viyana) sunulmuştur.

Committee Approval: This study has been exempted from the approval of the ethics committee.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - NY, EE, OÇ; Design - NY, EE, OÇ; Supervision - NY; Resources - NY, OÇ; Materials - NY, OÇ; Data Collection and/or Processing - NY, EE; Analysis and/or Interpretation - NY, EE; Literature Search - NY; Writing Manuscript - NY, EE; Critical Review - NY, EE, OÇ.

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