

# Comorbidities, Clinical Features, and Prognostic Implications of Cancer Patients with Cerebrovascular Disease

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*Purpose:* The objective of this study was to identify and describe the comorbidities, clinical features, and prognostic implications of cancer patients with cerebrovascular disease. *Materials and Methods:* All patients with cerebrovascular disease (CVD) seen in the neuro-oncology unit at a cancer referral center from April 2010 to November 2016 were included; demographic, oncologic diagnosis, risk factors, and prognostic considerations were presented as well. *Results:* We report on 256 patients with CVD and cancer, of whom 66% were women. The mean age at the time CVD occurred was 56 years. The most frequently associated malignancies were gynecologic (including breast cancer), hematologic, head and neck, and urologic. The men had more smoking and alcohol consumption history, hemorrhagic CVD, and urologic and hematologic malignancies. The women, besides gynecologic cancer, had more ischemic CVD. Thrombotic CVD, followed by embolic and hemorrhagic CVDs, was more frequent. A comorbid condition besides cancer was found in 71% of the patients. The most frequent clinical presentation was focal motor weakness, altered mental status, and aphasia. The 10-year mortality was 59%; higher rates were found in men, in those with hemorrhagic CVD, in tobacco users, and in those with altered mental status. *Conclusions:* Cancer is a well-known risk factor for stroke, which has been associated with a higher frequency in cancer. We found that ischemic stroke due to thrombosis and cardioembolism was more common, and gender, comorbidities, clinical presentation, and type of CVD, but not cancer type, were elements associated with prognosis. **Key Words:** Cancer—cerebrovascular diseases—stroke—prognostic—cryptogenic.  
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## Introduction

Stroke is the second leading cause of death after ischemic heart disease and the third leading cause of

disability-adjusted life years lost worldwide.<sup>1</sup> Cerebrovascular disease (CVD) is second only to metastases as a cause of central nervous system pathology in patients with cancer.<sup>2-4</sup> The incidence of stroke in patients with cancer has been reported to be 14.6%-30.0%<sup>1,3,5</sup> higher than that in the general population,<sup>2-4,6,7</sup> and there is an increased incidence of newly diagnosed malignancy in patients with stroke,<sup>8</sup> suggesting that it may be a presenting sign of systemic malignancy<sup>9</sup> and that cancer ought to be considered a major acquired prothrombotic disorder that predisposes patients to CVD.<sup>10,11</sup> CVD in patients with cancer may occur as (1) cerebral infarction owing to thrombosis, vessel compression or infiltration, treatment-related CVD, embolism, coagulopathy, venous sinus thrombosis, infection, radiation-induced vasculopathy; or (2) intracranial hemorrhage due to coagulopathy, vascular

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endothelial growth factor and vascular endothelial growth factor receptor inhibitors, tumor-related CVD, head trauma, and therapeutic anticoagulation.<sup>12,13</sup>

## Materials and Methods

A computerized database was prospectively collected from April 2010 to November 2016; patients with CVD seen by the neuro-oncology unit at a cancer referral center, whose clinical chart was completed and seen at least by one of the members of the department, were included. For all patients, age; gender; oncologic diagnosis; and stroke risk factors, including hypertension, diabetes mellitus, dyslipidemia, cardiac disease, tobacco and alcohol consumption, family history of stroke, and previous thrombotic events, follow-up, and mortality, were also analyzed. Gynecologic malignancy—for the purpose of the present article—included breast, uterine cervix, endometrial, and ovarian cancers; urologic malignancies included renal, bladder, and prostate cancers.

All patients' vital signs were noted, and Doppler ultrasound (carotid and vertebral basilar), electrocardiogram, lipid profile, glucose, HbA1c, and magnetic resonance imaging with arterial (magnetic resonance angiography) and venous (magnetic resonance venography) sequences were done as initial evaluation; for cryptogenic etiology to be considered as a cause of stroke, the abovementioned studies plus echocardiogram, blood cultures, and prothrombotic blood tests had to yield negative results.

### Statistical Analysis

Clinical manifestations, etiology, cancer type, comorbidities, and so on, were compared using the Student *t*-test and the Mann-Whitney *U*-tests for continuous variables. Analysis of variance and Tukey correction were used to analyze more than 3 variables, and the odds ratio was used to compare prognostic observations. Kaplan-Meier survival curves and the log-rank test were used to study survival; a 95% confidence interval was used, and a *P* value less than .05 was considered statistically significant. The local institutional review board (scientific and ethics committee) approved all interventions.

## Results

We reported on 256 patients with cancer and CVD, 168 women (66%) and 88 men (34%), with a mean age of  $56 \pm 16$  years (range 17-90) at the time CVD was diagnosed, higher in women ( $57 \pm 14$ ) than in men ( $53 \pm 19$ ) ( $P = .04$ ). The most frequent malignancies associated with CVD were gynecologic ( $n = 100$  [39%]), followed by hematologic (18%), head and neck (12%), urologic (11%), and gastrointestinal (8%) (Table 1).

Gender differences included older age, diabetes, ischemic stroke, and gynecologic cancers in women, whereas

men had a higher frequency of hematologic and urologic cancers, hemorrhagic stroke, and smoking and alcohol use.

Globally, CVD was ischemic in 72% of the patients, hemorrhagic in 27%, and cerebral venous thrombosis in 1% (Table 1). According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, the most common etiologic subtypes of ischemic stroke were large-vessel disease (36%) and cardioembolic stroke (27%); in 13%, no potential mechanism was identified and therefore considered cryptogenic. Unusual causes of ischemic stroke were found in 12 patients, mainly related to surgical intervention or the use of tyrosine kinase inhibitor (TKI).

Hemorrhagic strokes were found in 68 patients; 47 were parenchymal and 16 were extraparenchymal (10 subdural hematomas and 6 subarachnoid hemorrhages), 3 patients had parenchymal hemorrhage with an extension to the subarachnoid space, and 2 patients had hemorrhagic metastases.

Ischemic strokes were associated more frequently with gynecologic cancer ( $P = .02$ ), whereas hemorrhagic stroke was particularly common in patients with hematologic ( $P = .002$ ) and urologic malignancies ( $P = .03$ , Table 2).

A comorbid condition, besides cancer, was found in 182 patients (71%, Table 1). The most frequent comorbidities were high blood pressure (39%), overweight, and diabetes. Dyslipidemia, hypertension, and diabetes were associated with ischemic stroke, whereas no precise comorbidity was more commonly associated with hemorrhagic stroke (Table 2).

The most frequent clinical presentation of CVD was focal motor weakness ( $n = 171$ , 67%), followed by altered mental status ( $n = 91$ , 36%), aphasia or speech disorder ( $n = 74$ , 29%), visual defect or diplopia (25%), headache (22%), seizures (18%), ataxia (14%), and sensitive complaints (12%).

A 10-year follow-up was done with a case fatality rate of 59% (152 patients died). The mean overall survival was different according to the CVD type, and hemorrhagic strokes carried the worst prognosis (Table 3). Bivariate analysis showed a higher mortality for hemorrhagic stroke (76%) than for ischemic stroke (54%) and CVT; a trend toward higher mortality rates was found for men (67%). Other variables associated with higher mortality were not having dyslipidemia or diabetes, tobacco use, and altered mental status at the time of CVD. After the multivariate analysis, hemorrhagic CVD, absence of dyslipidemia or diabetes, alcohol use, and altered mental status remained statistically associated with greater mortality (Table 3).

## Discussion

Previous reports of CVD in patients with cancer are usually postmortem<sup>14-18</sup>; the present study is a prospectively acquired series of patients seen at an urban tertiary

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