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Current Problems in Cancer

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## Clinical presentation, risk factors and outcome of central nervous system metastasis vs stroke in cancer patients



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### A B S T R A C T

**Background and purpose:** Cancer and stroke are the second and third causes of death worldwide; brain metastases (BM) occur in one third of patients with cancer, any neurologic deficit in these population always prompts the clinician to discard metastases for their presence carries a bad outcome. Both might share clinical presentation and differences in their outcome are not entirely known. The aim was to compare risk factors, clinical presentation, and outcome of cancer patients with BM vs stroke.

**Methods:** A descriptive study with prospectively acquired data from a cancer referral center included patients seen at the neuro-oncologic unit from March 2011 to February 2018 with confirmed cancer who had BM or stroke.

**Results:** Six hundred and thirteen BM patients were compared with 268 with stroke and cancer. Demographic factors, cancer type, risk factors, clinical presentation, and outcome are presented. Median overall survival in months for those with any stroke was 15 (95%confidence interval [CI] 8.6-21.4)–5 (95%CI 0.12.4) for hemorrhagic stroke and 22 (95%CI 13.4-30.6) in the ischemic group—and for those with BM 12 (95%CI 10.4-13.6). Hemorrhagic stroke commonly found in stroke patients as well as focal motor weakness, aphasia, and altered mental status. BM was more common in breast and lung cancer with headache, visual complaint, and/or vertigo.

**Conclusion:** Survival in cancer patients with BM is not that different than those with stroke, but clinical presentation and risk factors were found different.

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\* Conflicts of interest: All authors declare that they have no conflicts of interest.

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## ARTICLE INFO

*Keywords:* Central nervous system metastases; Stroke; Survival; Risk factor; Prognosis

## Introduction

From a clinical standpoint, cancer could be a very complicated entity rarely having any distinctive characteristic. Which usually leads up to delays on diagnosis. One of the most feared complications that could arise from a delayed diagnosis are the neurological. From sensitive impairment up to seizures or cerebral edema, neurological disorders are the source of a significant disability and mortality.<sup>1</sup> One that stand out from the others are the brain metastases (BM). Although they could be originated from any type of cancer, especially after the better treatments favor longer survival of cancer patients, they usually are secondary to primary cancers like lung, breast, and melanoma.<sup>2,3</sup> The importance of BM is based on: its incidence, representing the most common malignancy on the brain<sup>4</sup> and occurring in up to 40% of patients with cancer<sup>2,5,6</sup>; and its widely association with a grim prognosis<sup>7,8</sup> with series having an overall survival of: 6.4 months<sup>9</sup>; 4.5 months;<sup>10</sup> and even 2.7-3.7 months.<sup>11</sup> That is why an early diagnosis and treatment is necessary.

The problem is that BM can manifest with a wide range of neurological manifestations, usually nonspecific,<sup>2,12</sup> but often quite severe,<sup>1</sup> and could be difficult to establish the diagnosis without further assessment in time; and while BM treatment it is hardly an emergency, there are other causes of neurological impairment that its treatment is an actual emergency.

According to the Global Burden of Disease study in 2015,<sup>13</sup> stroke was the third cause of death around the world, only behind ischemic heart disease and cancer. With an incidence increase of 68% (from 10 million to almost 17 million) between 1990 and 2010 it has become a rising problem albeit its mortality rate has diminished, the total numbers keep growing.<sup>14</sup> So, we have got 2 epidemiologically growing diseases that easily could be mistaken from one another as both can be manifested as a wide range of neurological symptoms. Both being common sources of disability, morbidity, and mortality and having a high impact on their daily activities and economic burden.<sup>15-17</sup> But not only the clinical manifestation makes the differentiation between them important, cancer and stroke also have been proved to have more associations as it has been established that stroke incidence is higher in cancer patients and the frequency of cancer is higher in those with stroke.<sup>18-22</sup> That is why, we thought appropriate to distinguish one from another as to our knowledge clinical manifestations and outcome, of those two conditions, are rarely compared.

## Material and methods

A preformatted computerized electronic database was created to prospectively collect data of patients of either sex with a cancer diagnosis, confirmed by the pathology department, who had a stroke or BM diagnosed by magnetic resonance imaging (MRI) studies who were evaluated by any of the members from the neuro-oncology unit at the National Cancer Institute, Mexico City from March 2011 to February 2018. The following variables obtained directly from the patients, relatives, or the clinical chart at the time of consultation: age at the time of stroke or BM diagnosis, cancer type, comorbid conditions including known risk factors for stroke, clinical symptoms/signs, follow-up duration, and outcome. Comorbidities included diabetes mellitus based on the American Diabetes Association criteria,<sup>23</sup> hypertension according to the eight Joint National Committee criteria,<sup>24</sup> dyslipidemia based on total cholesterol level above 200 mg/dL or triglyceride level above 159 mg/dL, overweight (body mass index 25-29 kg/m<sup>2</sup>) and obesity

(body mass index  $> 30\text{kg/m}^2$ ). A BM was considered if a MRI showed any lesion in the brain, brainstem, or cerebellum. Stroke was confirmed with MRI. Patients with wither stroke or BM not initially treated at our center were excluded. The institutional ethics and investigation committee approved data acquisition (INCAN/CI/837/17) waiving the need for written consent given the characteristics of the study.

### Statistical analysis

Differences among groups were analyzed with chi-square or Fisher test according to the variable type. A standard normal deviate ( $z$ -value) was calculated as  $\ln(\text{RR})/\text{SE}\{\ln(\text{RR})\}$ , and the  $P$  value was determined as the area of the normal distribution that falls outside  $\pm z$ ; 95% confidence interval (CI) was used and a  $P$  value  $< 0.05$  was considered as statistically significant. Survival was compared using Kaplan-Meier curves with log rank test.

## Results

A total of 881 patients with cancer were included in the present study, 268 (30%) had a stroke and 613 (70%). Median age at the time of stroke was higher than BM (58 vs 51 years)  $P < 0.001$ , no gender differences were found. General characteristics of both groups are presented in Table 1, cancer type most commonly associated with stroke were gynecologic, hematologic, head and neck, and gastrointestinal ( $P < 0.05$ ). Primary cancers more commonly associated with BM were breast and lung ( $P < 0.001$ ). Risk factors were more commonly associated with stroke than BM, mainly diabetes, dyslipidemia, hypertension, and overweight ( $P < 0.001$ ); but not obesity, alcohol, or smoking symptoms more frequently found in stroke than in BM were focal motor weakness, aphasia, and altered mental status ( $P < 0.001$ ). Symptoms more frequent in BM than stroke were: Headache, visual complaint, vertigo ( $p < 0.0001$  for each symptom), and abnormal movement disorders ( $P 0.029$ ).

Median overall survival (MOS) of patients with stroke was 15 months (95%CI 8.6-21.4 months), 22 (95%CI 13.4-30.6 months) for those with ischemic and 5 months (95%CI 0-12.4 months) for those with hemorrhagic stroke; MOS for the BM group was 12 months (95%CI 10.4-13.6 months)  $P < 0.001$  (Fig. 1).

## Discussion

We found in this large series that cancer patients with stroke had statistically but probably not clinically different outcome from those with BM. In the stroke group cardiovascular risk factors mainly diabetes, dyslipidemia, hypertension, and overweight were more common. Clinical presentation was also different, patients with stroke had higher rates of focal motor weakness, aphasia, and altered mental status. Among the studied groups, hemorrhagic stroke conveyed the worst prognosis.

We sought for literature on the subject over PubMed as “cranial metastases and stroke” founding 27 articles, “CNS metastases and stroke” finding 17 and “BM and stroke” finding 214. It is worth mentioning, though, that most of them are focused on stroke mimics (or chameleons) and rarely assess or do direct comparisons with BM. And even those who focus a little bit more on both BM and stroke, do so from an imaging point of view,<sup>25,26</sup> which implies the need of a better characterization of these conditions as they mention the difficulty that often comes from distinguishing them. And as we state earlier both BM and stroke are growing in importance given their epidemiology and are quite complex.

To this day, and after decades of research, BM keep bringing up a lot of interrogates. From its true incidence that as we describe before can varies from 15% to 40% on cancer patients<sup>1</sup>; their presentation typically overlooked; diagnosis, done with Magnetic Resonance Imaging with

**Table 1**  
Characteristics of study group

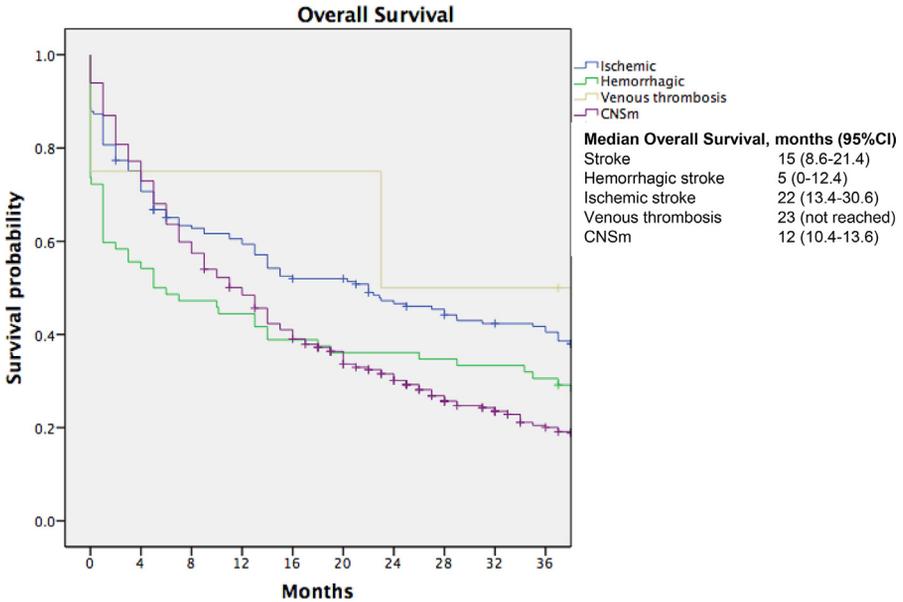
Characteristic	Stroke n (%)	BM n (%)	P
Median age (range) years	58 (17-90)	51 (17-85)	<0.001
Gender			
Female	176 (66)	435 (71)	0.14
Male	92 (34)	177 (29)	0.10
Primary cancer			
Breast	52 (19)	213 (35)	<0.001
Gynecologic	52 (19)	58 (10)	<0.001
Lung	20 (8)	134 (22)	<0.001
Hematologic	47 (18)	58 (10)	<0.001
Head and neck	31 (12)	42 (7)	0.011
Urologic	29 (11)	58 (10)	0.52
Gastrointestinal	24 (9)	16 (3)	<0.001
Sarcoma and soft tissue	12 (5)	26 (4)	0.87
Unknown primary	1 (0.4)	8 (1.3)	0.28
Clinical presentation			
Headache	59 (22)	318 (52)	<0.001
Focal motor weakness	176 (66)	198 (32)	<0.001
Focal sensitive complaint	33 (12)	72 (12)	0.44
Visual complaint/diplopia	65 (22)	230 (38)	<0.001
Seizure	46 (17)	133 (22)	0.07
Aphasia/speech disorder	76 (28)	71 (12)	<0.001
Altered mental status	96 (36)	130 (21)	<0.001
Ataxia	36 (13)	78 (13)	0.43
Abnormal movements	-	10 (2)	0.026
Vertigo	-	50 (8)	<0.001
Median survival (95%CI) months	15 (8.6-21.4)	12 (10.4-13.6)	<0.001
Comorbidity			
Present	191 (71)	323 (53)	<0.001
Diabetes	67 (25)	55 (9)	<0.001
Hypertension	104 (39)	117 (19)	<0.001
Dyslipidemia	56 (21)	23 (4)	<0.001
Overweight	96 (36)	138 (23)	<0.001
Obesity	46 (17)	127 (21)	0.13
Smoking	86 (32)	188 (31)	0.37
Alcohol use	65 (24)	119 (19)	0.06

BM, brain metastases.

quite a few differentials<sup>25,26</sup>; and the ideal treatment that keeps posing a lot of difficulties.<sup>11</sup> But one that stands over the others because of its implication it is the prognosis. From admittedly old reports with MOS of 33 days<sup>6</sup> and 4.5 months<sup>10</sup> to more recent and bigger reports<sup>9,11</sup> with MOSs of 2.7-3.7 months and 6.4 months, respectively; up to our median survival of 12 months, which could be better but it is far from ideal.

Even with all the research around stroke, and all the achievements in the field; there are still plenty of questions surrounding it. Questions that considerably multiply when considered in cancer patients, and its importance as cancer itself is rising. An autopsy series<sup>27</sup> found that 15% had some sort of lesion suggesting stroke, despite any symptoms could or could not have been referred. Other studies founded a large incidence in breast cancer patients referring up to 30% of affected patients with stroke.<sup>28</sup> And another study found out that from all strokes hospitalized, around 10% also happened to be oncologic patients.<sup>22</sup> Even a control-case study showed up a higher cumulative incidence rate in patients with lung cancer (5.1% vs 1.2%), pancreatic cancer (3.4% vs 1.3%), colorectal cancer (3.3% vs 1.3%), and breast cancer (1.5% vs 1.1%).<sup>29</sup> Also, it is well known that stroke can be the first manifestation of a concealed cancer.<sup>30-32</sup>

Regarding the etiology, it is necessary to mention that compared to the general population, the cryptogenic origin of stroke, were its incidence is up to 30%; in cancer patients could reach up to 50% of the cases.<sup>33,34</sup> And, it has been described as a potential risk factor for a worse prognosis.<sup>35</sup> But from the known etiology, ischemic stroke represents 86% of the cases, leaving hemorrhagic stroke to represent only 14%.<sup>36</sup>



**Fig. 1.** Comparison of survival according to the diagnosis of stroke subtype and central nervous system metastases (CNSm).

About the primary cancer in ischemic stroke cases, it is poorly defined, showing a wide variety of tumor types.<sup>37</sup> Some series put lung, brain, and prostate<sup>38</sup> as the more common, others do Gastrointestinal, lung, and skin<sup>39</sup> and others Gynecologic, renal, and gastrointestinal.<sup>40</sup> While the hemorrhagic stroke is more frequently, and uniform, secondary to hematologic neoplasms. Mainly leukemia with up to 72% of strokes are hemorrhagic over lymphoma were only 36% are hemorrhagic.<sup>20</sup>

Clinically it is agreed upon the most common features in stroke are hemiparesis, speech disturbance, and/or visual impairment.<sup>37,41</sup> However, because of the common embolic etiology, characterized by multifocal infarcts, encephalopathy it is also common among these patients.<sup>42</sup>

In the general population the mortality rates after ischemic stroke are 15% at 1 month, 25% at 1 year, and 50% at 5 years; and in hemorrhagic are 55% at 5 years and 70% at 5 years.<sup>14</sup> The only reported mean overall survival of ischemic stroke in cancer patients we found was 174 days (~5.8 months) with known mechanism and 55 days (~1.8 months) in cryptogenic.<sup>43</sup> Which we narrowly surpassed with 15 months.

Stroke, by itself, remains an understudied problem that seems far to be solve, especially (and worryingly) when it comes to its presence in cancer patients, as we found both in theory and practice, behaves differently enough to be further studied. And as for BM it should be clear, only by its prognosis, that further studies are needed as nowadays the information is scarce and in desperate need of an update.

**Conclusion**

In cancer patients, stroke and brain metastases are common and carry a poor prognosis. Cancer type, cardiovascular risk factors and clinical presentation are different. Further studies are encouraged to improve diagnosis and treatment of both lethal conditions.

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