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Temporal Trends in the Use of Acute Recanalization Therapies for Ischemic Stroke in Patients with Cancer

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Declaration of Conflicting Interests
The authors declare that they have no conflict of interest.

Abstract

Objective: We sought to characterize the United States nationwide temporal trends in recanalization therapy utilization for ischemic stroke among patients with and without cancer.

Methods: We identified all acute ischemic stroke hospitalizations in the National Inpatient Sample from January 1, 1998-September 30, 2015. The primary exposure was solid or hematologic cancer. The primary outcome was use of intravenous thrombolysis. The secondary outcome was use of endovascular therapy.

Results: Among 9,508,804 acute ischemic stroke hospitalizations, 503,510 (5.3%) involved cancer patients. Intravenous thrombolysis use among ischemic stroke patients with cancer increased from 0.01% (95% CI, 0.00–0.02%) in 1998 to 4.91% (95% CI, 4.33–5.48%) in 2015; while intravenous thrombolysis use among ischemic stroke patients without cancer increased from 0.02% (95% CI, 0.01–0.02%) in 1998 to 7.22% (95% CI, 6.98–7.45%) in 2015. The demographic- and comorbidity-adjusted odds ratio/year of receiving intravenous thrombolysis was similar in patients with cancer (1.21; 95% CI, 1.20–1.23) versus those without (1.20; 95% CI, 1.19–1.21). Endovascular therapy use among ischemic stroke patients with cancer increased from 0.05% (95% CI, 0.02–0.07%) in 2006 to 1.90% (95% CI, 1.49–2.31%) in 2015; while endovascular therapy use among ischemic stroke patients without cancer increased from 0.09% (95% CI, 0.00–0.18%) in 2006 to 1.88% (95% CI, 1.68–2.09%) in 2015.

Conclusions: Among 9.5 million acute ischemic stroke hospitalizations, patients with cancer received intravenous thrombolysis about two-thirds as often as patients without cancer. This difference persisted over time despite increased utilization in both groups. Endovascular therapy utilization was similar between cancer and non-cancer acute ischemic stroke patients.

Keywords

cancer; ischemic stroke; thrombolysis; endovascular therapy; recanalization therapy; oncology

Introduction

Acute ischemic stroke (AIS) is associated with substantial morbidity, particularly when caused by a large vessel occlusion.(1) Two proven treatments for AIS are intravenous tissue plasminogen activator (IV-tPA) and endovascular therapy (EVT).(2) IV-tPA was first shown to be beneficial in AIS in 1995,(3) while the first positive AIS EVT trial was in 2014.(4) These acute recanalization therapies significantly increase the odds of a good neurological outcome at 3 months, especially if recanalization is achieved.(5, 6) Consequently, utilization of these therapies has gradually increased over time, contributing, in part, to lower rates of death and disability from AIS.(7, 8)

Like stroke, cancer is a common and often morbid disease. In the United States, two of every five persons are expected to develop cancer in their lifetime.(9) These individuals face an increased risk of stroke,(10) especially in the first 6 months after cancer diagnosis.(11) Cancer-mediated hypercoagulability is presumed to account for much of this increased stroke risk. Potential mechanisms of cancer-mediated hypercoagulability include circulating procoagulant microparticles, platelet overactivation, tissue factor overexpression,

coagulation factor derangements, and neutrophil extracellular trap formation.(12–15) Prothrombotic effects of chemotherapy and reductions in antithrombotic use may also contribute to the link between cancer and AIS.(16) Furthermore, 5–10% of patients with AIS have comorbid cancer and this frequency is expected to increase with continued advances in cancer survival.(16–18)

Most clinical trials evaluating recanalization therapies for AIS excluded patients with cancer, and therefore the effectiveness of these therapies in the cancer population is uncertain. Nevertheless, single-center case series and claims-based cohort studies suggest that selective use of these therapies in cancer patients who otherwise meet eligibility criteria may be safe.(19–21) Furthermore, neither the American Heart Association/American Stroke Association nor the United States Food and Drug Administration, per the product label for Alteplase, consider active cancer to be an absolute contraindication for IV-tPA or EVT for AIS.(22, 23) Therefore, these recanalization therapies are presumably being used in some cancer patients with AIS; however, the frequency of their use is uncertain. We sought to characterize the United States nationwide temporal trends in the use of IV-tPA and EVT among AIS patients with and without cancer. Because of limited data supporting the use of IV-tPA in the cancer population, as well as presumed increased contraindications, such as chemotherapy-induced thrombocytopenia,(24–26) our prespecified hypothesis was that there would be differences in utilization rates between cancer and non-cancer patients and that these disparities would widen over time.

Methods

Design

We used inpatient discharge data from the 1998 through 2015 releases of the Healthcare Cost and Utilization Project's (HCUP) National Inpatient Sample (NIS).(27) The United States NIS is a nationally representative deidentified dataset that is funded by the Agency for Healthcare Research and Quality (AHRQ), and includes data from a 20% stratified probability sample of community hospitals participating in HCUP. Each discharge record includes 1 primary diagnosis code, up to 29 secondary diagnosis codes, 1 primary procedure code, and up to 14 secondary procedure codes, all of which are assigned according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) system. The Weill Cornell Medicine institutional review board approved the analysis of these data and waived the need for informed consent. We adhered to recommended guidelines for best research practices when using the NIS.(28) The data used in this analysis includes restricted NIS claims data and therefore cannot be shared directly with other investigators because of the terms of the data use agreement. However, investigators can obtain access to these data by application to the AHRQ.

Population

We identified all hospitalizations for AIS from January 1, 1998 through September 30, 2015, defined by the presence of *ICD-9-CM* diagnosis codes 433.xx, 434.xx, or 436 in any position in the absence of codes for trauma or a code for rehabilitation in the primary position. This validated diagnosis code algorithm was previously shown to have a positive

predictive value greater than 90%.(29) We did not evaluate hospitalizations after September 30, 2015 due to the adoption of *ICD-10* in the United States after that date.

Measurements

The primary exposure was the presence of comorbid systemic cancer. Our approach to identifying systemic cancer has been previously described, and consisted of a composite of solid tumors without metastases (140.xx-190.xx, 193.xx-195.xx, 209.00–209.30), hematologic tumors without metastases (200.xx-208.xx, 238.7x), and metastatic solid or hematologic tumors (196.xx-198.xx, 209.7x).(20) Patients with primary brain tumors were excluded. The primary outcome was the use of IV-tPA, which was defined as the presence of *ICD-9-CM* procedure code 99.10; and the secondary outcome was the use of EVT, which was defined as the presence of *ICD-9-CM* procedure code 39.74. Data were also collected on patients' demographics and relevant comorbidities.

Statistical Analysis

Descriptive statistics were used to evaluate patient characteristics. Depending on data distribution, continuous variables were compared with Student's t-test or the Wilcoxon rank sum test and categorical variables were compared with the chi-square test or Fisher's exact test. Sampling weights provided by the NIS were used to obtain United States national estimates for all outcomes. We used the updated "trend" weights for the period between 1998–2011 and the original discharge weights for 2012–2015 (in order to account for the NIS sampling redesign in 2012). Annual rates of acute recanalization therapy use were calculated among AIS hospitalizations involving patients with and without cancer. Because a procedure code for EVT first became available in 2006, we do not report EVT utilization rates before then. Variance-weighted linear least squares regression was used to test for temporal trends. All trend analyses were two-tailed and used an alpha error of 0.05.

To evaluate the associations between time and our outcomes, we also created multivariable logistic regression models adjusted for age, sex, race/ethnicity, and stroke risk factors that included the year of hospitalization as a covariate. Subgroup analyses were performed among patients with different cancer subtypes and among patients treated at teaching hospitals. For the cancer subtype analyses, patients could have both non-metastatic solid tumors and non-metastatic hematologic tumors; however, if patients had diagnosis codes for both non-metastatic tumors and metastatic tumors, they were assigned to the metastatic group. Statistical analyses were performed using Stata (version 14.0, College Station, TX).

Results

Patient Characteristics

Among 9,508,804 hospitalizations for AIS in the United States between January 1, 1998 and September 30, 2015, 503,510 (5.3%) involved patients with diagnoses of comorbid cancer. Approximately 65% of these patients had non-metastatic solid or hematologic cancers while the remainder had metastatic cancers. Compared to patients without cancer, patients with cancer were more often older, male, white, and had chronic obstructive pulmonary disease but less often had diabetes mellitus, hypertension, and coronary artery disease (Table 1).

Among patients with cancer, those who received recanalization therapies were generally younger and had more stroke risk factors (Table 2).

Intravenous Thrombolysis Utilization

Overall rates of IV-tPA use throughout the study period were 2.0% (95% confidence interval [CI], 1.9–2.1%) among AIS patients with cancer versus 3.2% (95% CI, 3.1–3.3%) among AIS patients without cancer. The rate of IV-tPA use among AIS patients with cancer increased from 0.01% (95% CI, 0.00–0.02%) in 1998 to 4.91% (95% CI, 4.33–5.48%) in 2015 ($p<0.001$ for trend); while the rate of IV-tPA use among AIS patients without cancer increased from 0.02% (95% CI, 0.01–0.02%) in 1998 to 7.22% (95% CI, 6.98–7.45%) in 2015 ($p<0.001$ for trend) (Figure 1). In multivariable analysis, the demographic- and comorbidity-adjusted odds ratio per year of receiving IV-tPA was similar in patients with cancer (1.21; 95% CI, 1.20–1.23) versus those without (1.20; 95% CI, 1.19–1.21).

Endovascular Therapy Utilization

From January 1, 2006 through September 30, 2015, overall rates of EVT use for AIS were 0.7% (95% CI, 0.7–0.8%) among patients with cancer versus 0.8% (95% CI, 0.7–0.9%) among patients without cancer. The rate of EVT use among AIS patients with cancer increased from 0.05% (95% CI, 0.02–0.07%) in 2006 to 1.90% (95% CI, 1.49–2.31%) in 2015 ($p<0.001$ for trend); while the rate of EVT use among AIS patients without cancer increased from 0.09% (95% CI, 0.00–0.18%) in 2006 to 1.88% (95% CI, 1.68–2.09%) in 2015 ($p<0.001$ for trend) (Figure 2). In multivariable analysis, the demographic- and comorbidity-adjusted odds ratio per year of receiving EVT was similar in patients with cancer (1.20; 95% CI, 1.18–1.22) versus those without (OR, 1.19; 95% CI, 1.18–1.20).

Subgroup Analyses

Rates of IV-tPA use increased over time in all cancer patients regardless of cancer subtype ($p<0.001$ for trends), but were higher in AIS patients with non-metastatic solid or hematologic cancers than in those with metastatic cancers. Similarly, rates of EVT use also increased over time in all cancer patients regardless of cancer subtype ($p<0.001$ for trends), but were higher throughout the study period in AIS patients with non-metastatic solid or hematologic cancers than in those with metastatic cancers.

Rates of IV-tPA use were higher in teaching hospitals than in non-teaching hospitals ($p<0.001$); however, the difference in utilization rates between cancer (2.6%; 95% CI, 2.4–2.8%) and non-cancer patients (4.4%; 95% CI, 4.2–4.6%) persisted. Rates of EVT use were also higher in teaching hospitals than in non-teaching hospitals ($p<0.001$); however, unlike with IV-tPA, utilization rates were similar between cancer (1.0%; 95% CI, 0.9–1.2) and non-cancer patients (1.2%; 95% CI, 1.1–1.3%) at teaching hospitals.

Discussion

In a retrospective analysis of a large nationwide sample of inpatient hospitalizations from 1998–2015, we found that cancer patients with AIS received IV-tPA about two-thirds as often as non-cancer patients with AIS. Contrary to our prespecified hypothesis, this

difference in AIS IV-tPA use between cancer and non-cancer patients did not widen over time, as utilization rates increased about 20% per year in both groups. IV-tPA utilization rates were highest in patients without metastatic cancer and at teaching hospitals. In contrast, rates of EVT use for AIS were similar between cancer and non-cancer patients throughout the study period, and EVT utilization rates increased about 20% per year in both groups. EVT utilization rates were highest in patients without metastatic cancer and at teaching hospitals.

Several retrospective studies have evaluated IV-tPA and EVT use in cancer patients with AIS. These analyses concentrated on the risk of hemorrhagic complications and death, and most were small, single-center case series that lacked control groups.(19–21, 30, 31) These studies suggested that careful use of acute recanalization therapies in select cancer patients with AIS might be safe, as hemorrhage rates were similar to those from large randomized trials of predominantly non-cancer AIS patients.(3, 32) Our study, in contrast, was focused on temporal trends and disparities in stroke recanalization therapies between the cancer and non-cancer populations. As hypothesized, IV-tPA use was less frequent in AIS patients with cancer versus those without, although EVT use was surprisingly similar between groups. In this claims-based study, which lacked granular clinical data, we were unable to determine the reason(s) for this discrepancy; however, one possible explanation would be that compared to non-cancer patients, cancer patients might have had higher rates of exclusions for IV-tPA but not for endovascular therapy. For instance, thrombocytopenia, recent major surgery, intracranial lesions, and anticoagulant use are all exclusions for IV-tPA, as well as common scenarios in patients with cancer, but they generally do not exclude a patient from receiving EVT.(16, 33)

Alternative potential explanations for the discrepancy in utilization of IV-tPA and EVT include possible differences in physician factors, such as the goals of care of providers, or patient factors, such as premorbid functional status, perceived survival, stroke severity, stroke mechanisms, and access to stroke care between the cancer and non-cancer groups. Future prospective studies with detailed case ascertainment will be necessary to determine why cancer patients are one-third less likely to receive IV-tPA, but as likely to receive EVT, for AIS, than patients without cancer. The difference in IV-tPA use for AIS between cancer and non-cancer patients did not widen over the 17-year study period, and by 2015, nearly 5% of cancer patients with AIS were receiving thrombolysis treatment. It is important that patients with cancer have sufficient access to cutting-edge stroke care and treatments as they currently make up 5–10% of all stroke cases, and this co-prevalence is expected to increase with advances in cancer screening, molecular diagnostics, and targeted chemotherapy, including immunotherapy. In the United States, two-thirds of patients with cancer already survive more than 5 years from their diagnosis.(17)

This study has several limitations. First, it was a retrospective analysis of claims data, and therefore lacked information on patients' premorbid functional status and eligibility for recanalization therapies, cancer stage and treatments, stroke severity and mechanisms, presence of large vessel occlusions, time to treatment, devices used for EVT, and the attitudes of treating clinicians. Second, because of our reliance on diagnosis and procedure codes, there may have been misclassification of stroke diagnoses and treatments received.

We attempted to mitigate this concern by using previously validated algorithms for claims data.(29) Third, this study was restricted to patients in the United States and therefore its results may not generalize to other populations. Fourth, NIS captures hospitalization events, not individual patients; therefore, multiple observed events could have occurred in a single patient, which could have affected the precision of our estimated outcome rates.

In summary, from 1998–2015, patients with cancer in the United States were one-third less likely to receive IV-tPA for AIS as compared to patients without cancer. This difference in treatment rates persisted throughout the study period, although utilization rates increased by about 20% each year, and in 2015, at the end of study, nearly 5% of cancer patients with AIS received IV-tPA. Furthermore, patients with metastatic cancer were less likely to receive IV-tPA than those with non-metastatic solid or hematologic cancers. In contrast, patients with cancer were as likely to receive EVT for AIS as compared to patients without cancer, and utilization rates also increased by about 20% each year in both groups. Additionally, similar to IV-tPA utilization, patients with metastatic cancer were less likely to receive EVT than those with non-metastatic solid or hematologic cancers. Although frequently performed in clinical practice—as indicated in this analysis—future prospective studies should evaluate the safety and efficacy of AIS recanalization therapies in patients with cancer, particularly among those with metastatic cancer, who appear to have the highest risks of stroke.(10, 34)

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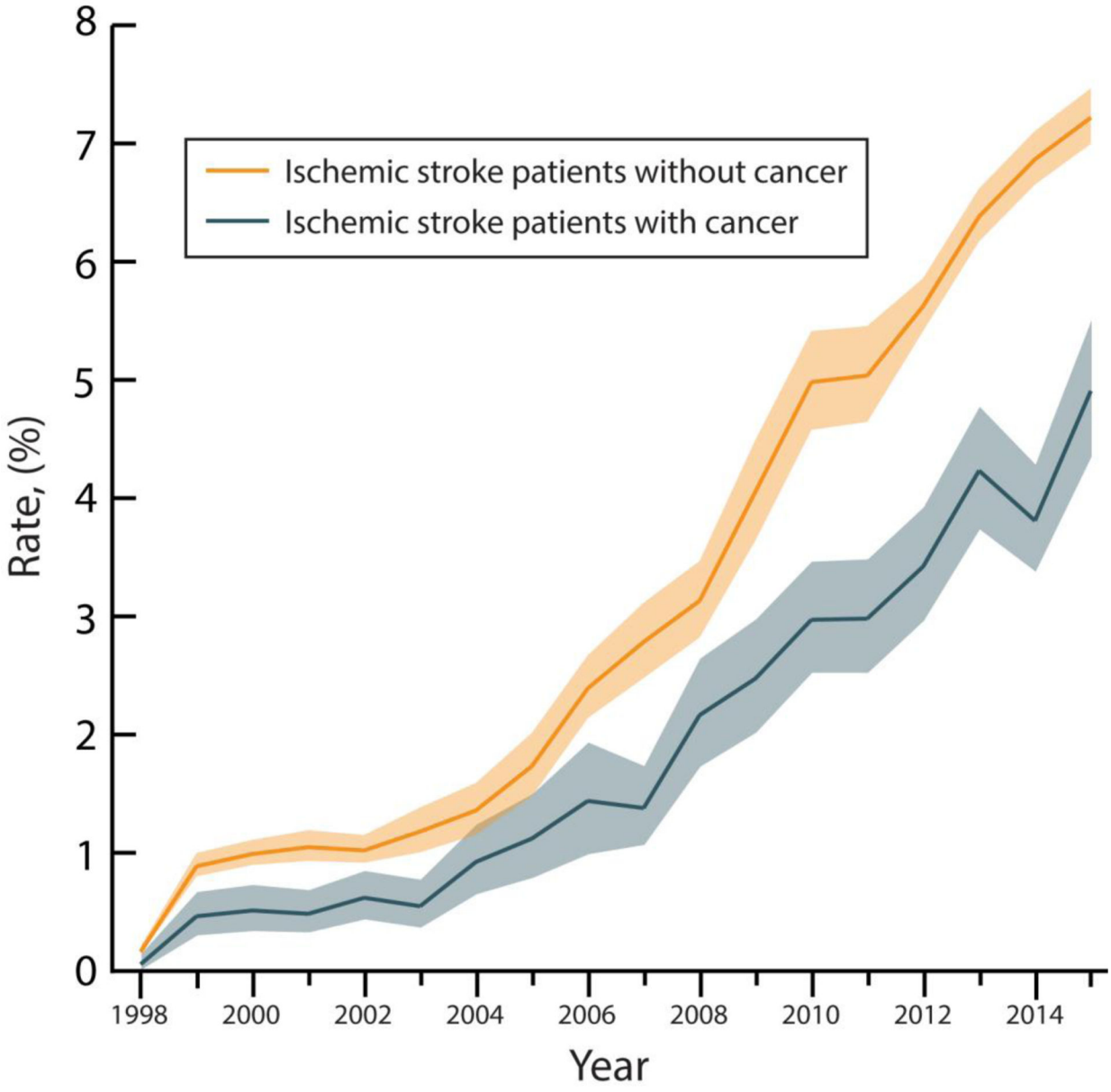


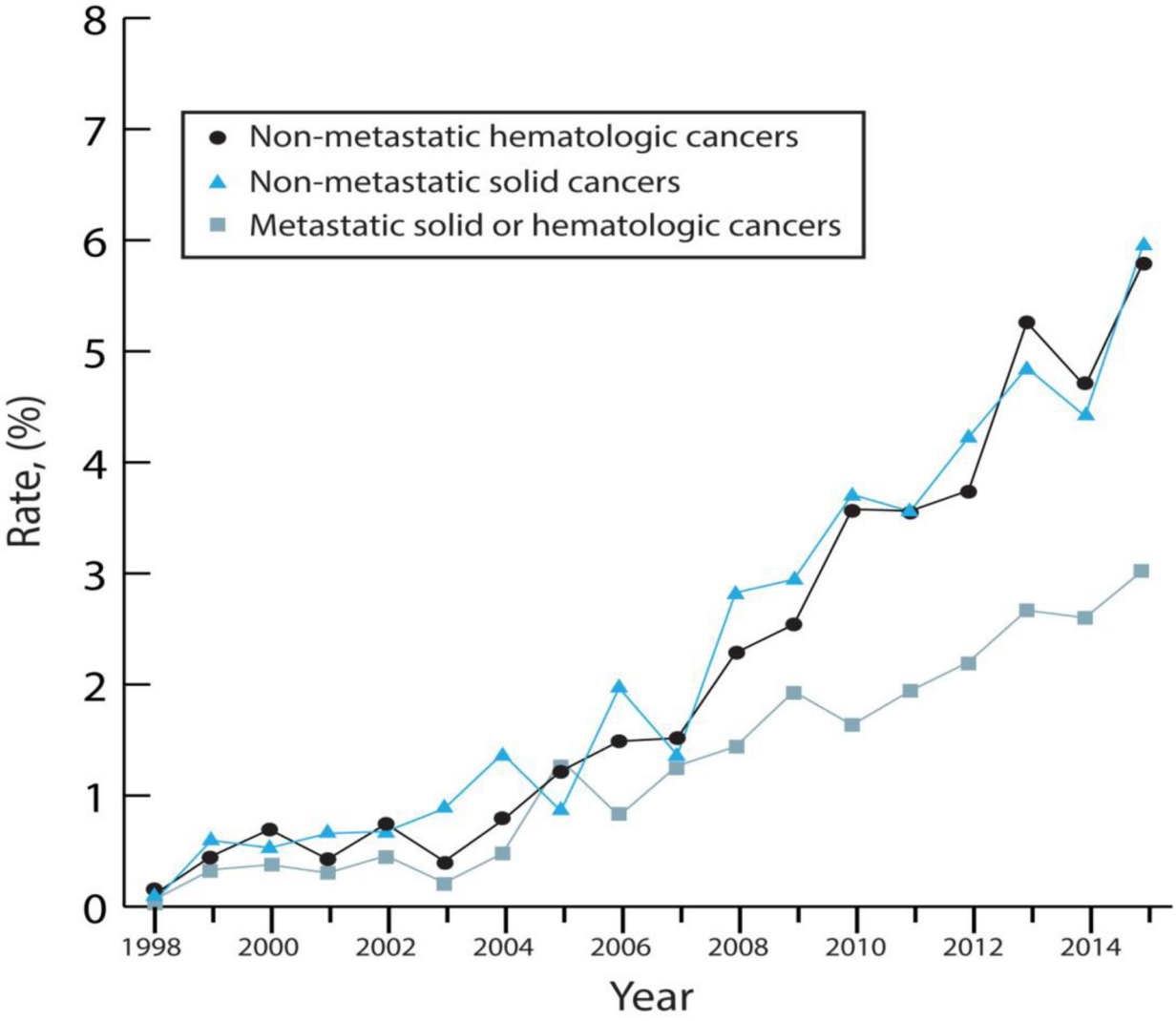
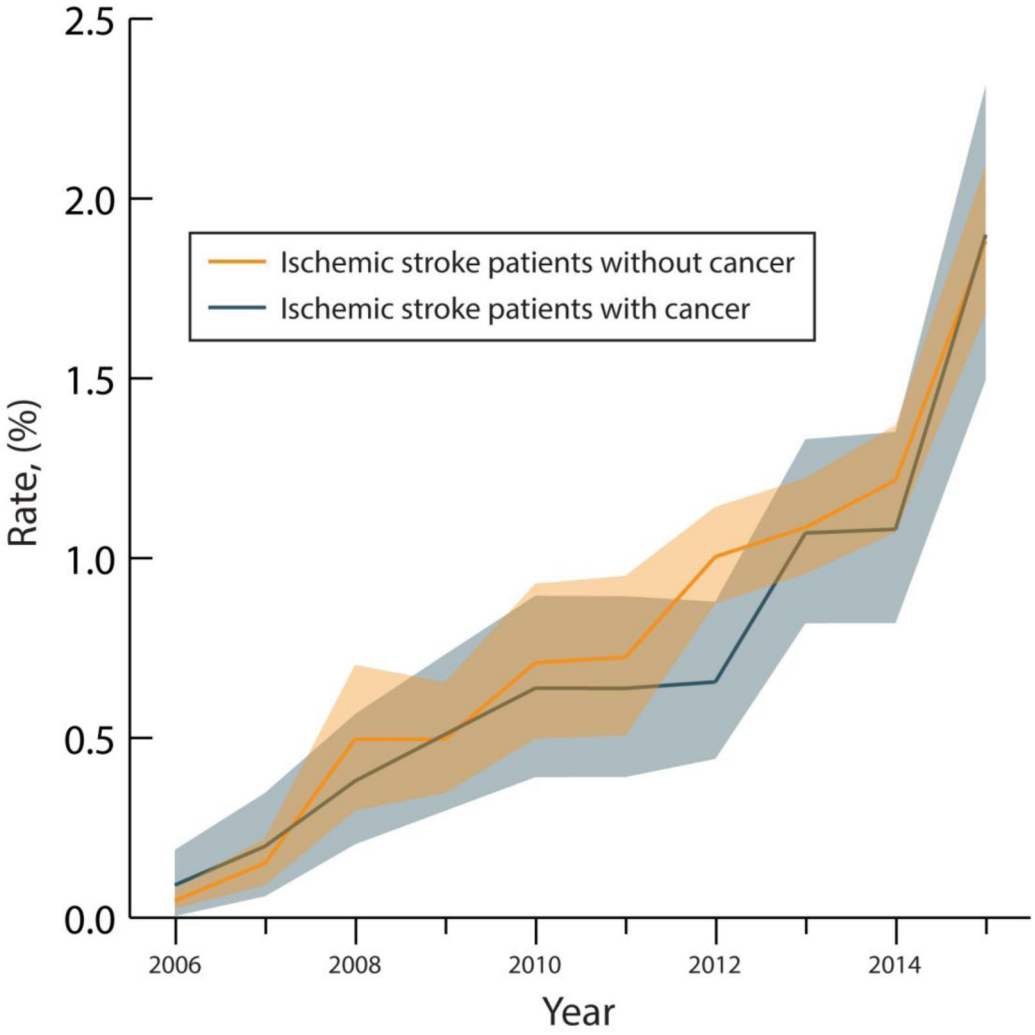


Figure 1.

A and B. Intravenous Thrombolysis Use Among Hospitalizations for Ischemic Stroke in the National Inpatient Sample, 1998–2015.

A. Annual rates of intravenous thrombolysis use among hospitalizations for acute ischemic stroke in the National Inpatient Sample from 1998–2015. Data is stratified by the presence of comorbid cancer. The lighter shade sections of the curves denote 95% confidence intervals.

B. Annual rates of intravenous thrombolysis use among hospitalizations for acute ischemic stroke in patients with cancer in the National Inpatient Sample from 1998–2015. Data is stratified by cancer type, including patients with non-metastatic hematologic cancers, non-metastatic solid cancers, and metastatic hematologic or solid cancers.



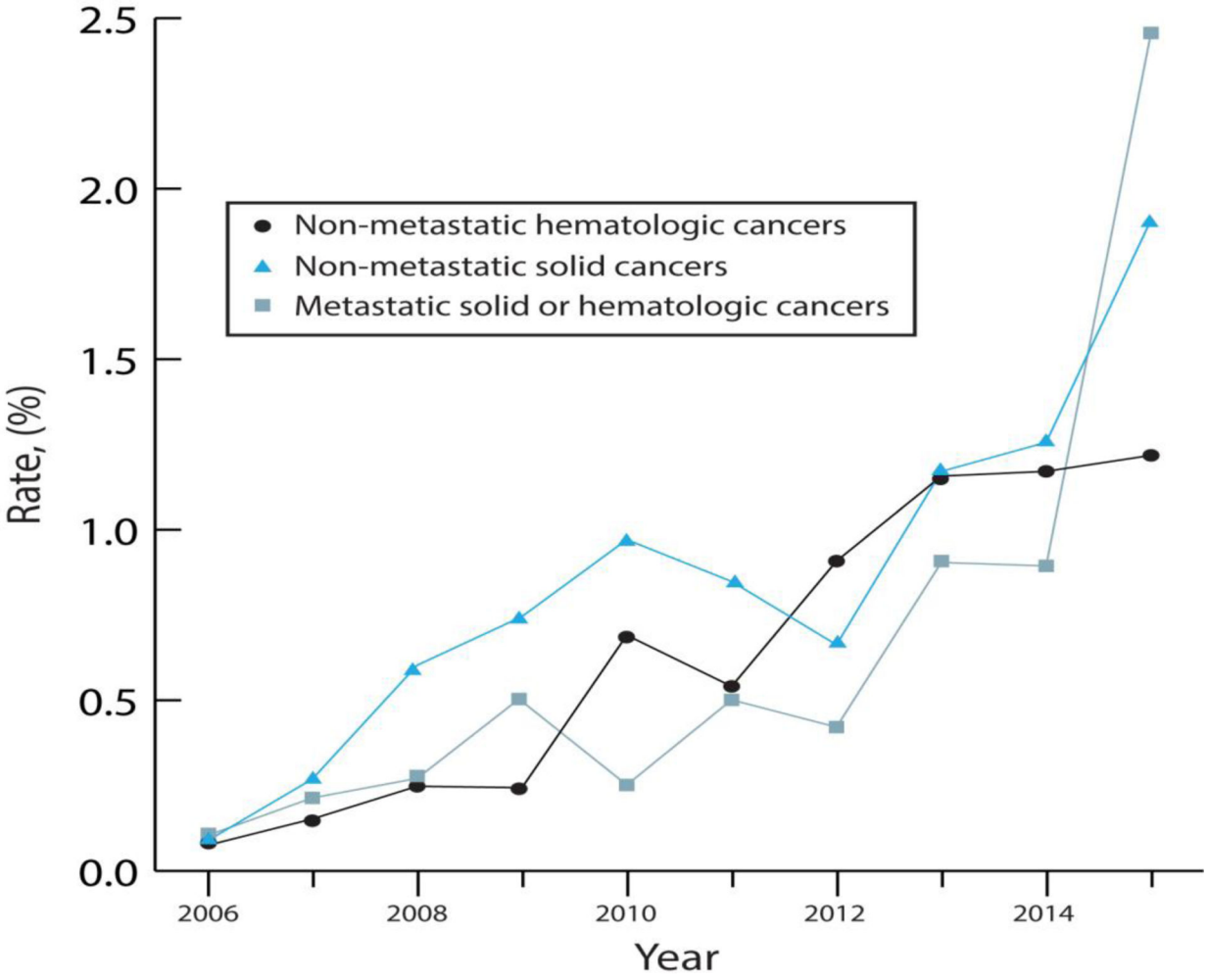


Figure 2.

A and B Endovascular Therapy Use Among Hospitalizations for Ischemic Stroke in the National Inpatient Sample, 2006–2015.

A. Annual rates of endovascular therapy use among hospitalizations for acute ischemic stroke in the National Inpatient Sample from 2006–2015. Data is stratified by the presence of comorbid cancer. The lighter shade sections of the curves denote 95% confidence intervals.

B. Annual rates of endovascular therapy use among hospitalizations for acute ischemic stroke in patients with cancer in the National Inpatient Sample from 2006–2015. Data is stratified by cancer type, including patients with non-metastatic hematologic cancers, non-metastatic solid cancers, and metastatic hematologic or solid cancers.

Table 1.

Baseline Characteristics of Patients with Hospitalization Events for Acute Ischemic Stroke, Stratified by the Presence of Cancer, 1998–2015

Patient Characteristics*	Cancer (n=503,510)	No Cancer (n=9,005,294)
Age, mean (SE)	72.8 (0.1)	71.3 (0.1)
Female sex	240,310 (47.7)	4,893,444 (54.3)
Race/Ethnicity		
White	324,017 (77.1)	5,272,625 (71.6)
Black	54,956 (13.1)	1,171,122 (15.9)
Hispanic	22,159 (5.3)	527,778 (7.2)
Asian	9,335 (2.2)	185,495 (2.5)
Native American	1,303 (0.3)	30,180 (0.4)
Other	8,704 (2.1)	173,718 (2.4)
Stroke Risk Factors		
Hypertension	224,172 (44.5)	5,087,769 (56.5)
Diabetes mellitus	115,982 (23.0)	2,842,414 (31.6)
Atrial fibrillation	107,733 (21.4)	1,989,726 (22.1)
COPD	106,416 (21.1)	1,373,119 (15.2)
Coronary artery disease	103,705 (20.6)	2,198,233 (24.4)
Tobacco use	98,187 (19.5)	1,670,867 (18.6)
Congestive heart failure	77,034 (15.3)	1,458,986 (16.2)
Acute myocardial infarction	51,932 (10.3)	904,969 (10.0)
Renal disease	48,750 (9.7)	804,300 (8.9)
Peripheral vascular disease	36,385 (7.2)	744,751 (8.3)
Liver disease	8,614 (1.7)	100,043 (1.1)
Charlson comorbidity score, mean (SE)	3.4 (0.01)	2.2 (0.004)

Abbreviations: SE, standard error; COPD, chronic obstructive pulmonary disease.

*All values are presented as No. (%) unless otherwise specified. Percentages may not add up to 100 because of rounding.

Table 2.

Baseline Characteristics of Patients with Cancer and Acute Ischemic Stroke Hospitalizations, Stratified by Use of Acute Recanalization Therapies, 1998–2015

Patient Characteristics*†	Endovascular Therapy (n=2,206)	Intravenous Thrombolysis (n=10,315)	No Recanalization Therapy (n=491,856)
Age, mean (SE)	68.3 (0.7)	72.1 (0.3)	72.8 (0.1)
Female sex	1,136 (51.5)	5,019 (48.7)	234,632 (47.7)
Race/Ethnicity			
White	1,454 (75.8)	7,065 (77.1)	316,022 (77.1)
Black	158 (8.3)	1,138 (12.4)	53,730 (13.1)
Hispanic	145 (7.6)	491 (5.4)	21,574 (5.3)
Asian	75 (3.9)	244 (2.7)	9,064 (2.2)
Native American	0 (0)	18 (0.2)	1,271 (0.3)
Other	85 (4.4)	202 (2.2)	8,449 (2.1)
Stroke risk factors			
Hypertension	1,116 (50.6)	5,240 (50.8)	218,254 (44.4)
Atrial fibrillation	757 (34.3)	3,313 (32.1)	103,945 (21.1)
Tobacco use	623 (28.2)	2,731 (26.5)	95,040 (19.3)
Diabetes mellitus	516 (23.4)	2,557 (24.8)	113,135 (23.0)
COPD	498 (22.6)	1,994 (19.3)	104,104 (21.2)
Coronary artery disease	464 (21)	2,386 (23.1)	101,048 (20.5)
Congestive heart failure	350 (15.9)	1,732 (16.8)	75,098 (15.3)
Acute myocardial infarction	313 (14.2)	1,107 (10.7)	50,616 (10.3)
Peripheral vascular disease	246 (11.2)	891 (8.6)	35,355 (7.2)
Renal disease	218 (9.9)	1,344 (13)	47,271 (9.6)
Liver disease	25 (1.1)	215 (2.1)	12,338 (2.5)
Charlson comorbidity score, mean (SE)	3.9 (0.06)	3.6 (0.03)	3.4 (0.01)
Cancer type‡			
Non-metastatic solid tumors	995 (45.1)	4,783 (46.4)	198,318 (40.3)
Non-metastatic hematologic tumors	576 (26.1)	3,271 (31.7)	123,481 (25.1)
Metastatic solid/hematologic tumors	681 (30.9)	2,391 (23.2)	173,921 (35.4)

Abbreviations: SE, standard error; COPD, chronic obstructive pulmonary disease.

*All values are presented as No. (%) unless otherwise specified. Percentages may not add up to 100 because of rounding.

†Some patients were treated with both endovascular therapy and intravenous thrombolysis. Endovascular therapy data is only provided from 2006 onward because that is when its procedure code first became available.

‡Numbers add up to more than the total denominator and percentages add up to more than 100 because some patients had both non-metastatic solid tumors and non-metastatic hematologic tumors. Patients who had diagnosis codes for metastatic and non-metastatic tumors were assigned to the metastatic group.