Original research

Endovascular thrombectomy for acute ischemic stroke in patients with cancer: a propensity-matched analysis

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ABSTRACT

Background There is a paucity of data and a belief that endovascular thrombectomy (EVT) has low efficacy for acute ischemic stroke (AIS) in patients with cancer. We aimed to critically compare the clinical outcomes of EVT for AIS in patients with and without cancer.

Methods Records of all patients undergoing EVT for AIS between January 2015 and 2020 were screened for cancer at the time of EVT. Active cancer was defined as patients who were diagnosed with cancer and were undergoing or refused treatment for that cancer. Baseline modified Rankin Scale (mRS), age and sex were used in a 1:5 propensity score matching ratio. After matching we evaluated for any change in the National Institutes of Health Stroke Scale (NIHSS) from baseline to discharge, hemorrhagic transformation (HT), and 90-day mRS and mortality.

Results There were 19 patients with cancer and 95 matched controls. The mean±SD age was 70.89±11.16 years, and 17 (89.47%) were female. The baseline NIHSS was 22±7.5 and baseline mRS was 1 (IQR 1). There was no significant difference in change in baseline to discharge NIHSS, 90-day mRS or mortality; 90-day mRS 0–2 was 45.2% in the non-cancer group versus 46.7% in cancer group (p=0.54). HT was significantly higher in patients with cancer (57.89% vs 6.49%, p<0.001).

Conclusions In propensity matched analysis of patients undergoing EVT for AIS with and without cancer, 90-day functional outcomes and mortality were similar. However, there was a significantly higher rate of HT in cancer patients.

INTRODUCTION

Along with poor baseline level of function, low Alberta Stroke Program Early CT Score (ASPECTS), low National Institutes of Health Stroke Scale (NIHSS) and older age, a history of active cancer was not only an exclusion criteria for the highly-cited EVT trials published in 2015, but is generally regarded as a marker for futile recanalization.[1 2] However, 15% of cancer patients can develop cerebrovascular disease,[3] which may involve cancer-associated hypercoagulable states, chemotherapy, or radiotherapy-related vasculopathy, and classical migratory thrombosis.[4–6] Intravenous thrombolysis using intravenous tissue plasminogen activator (IV-tPA) is relatively contraindicated for cancer patients because of the concern for hemorrhagic complications associated with intracranial metastasis.[2] As more studies are underway to evaluate the clinical effectiveness of thrombectomy in subgroups previously excluded from trials, such as those with cancer, a critical analysis of not only how this subgroup of patients is defined, but also their outcomes after thrombectomy, may provide guidance for thrombectomy patient selection for this subgroup.

Our study aimed to measure, by propensity analysis, whether active cancer influences angiographic and clinical outcomes for patients with large vessel occlusion undergoing EVT. Prior controlled studies have maintained a broad definition of active cancer, and commonly included all patients who were diagnosed with cancer and were undergoing or refused treatment for it. This operational definition best aligns with prior literature and allows us to address the precise subgroup previously excluded from prior randomized thrombectomy clinical trials.

METHODS

We conducted a retrospective chart review of all patients with acute ischemic stroke who underwent mechanical thrombectomy at a single, urban, tertiary care academic comprehensive stroke center. The study was approved by the local Institutional Review Board (IRB), which waived the requirement for informed consent due to the retrospective nature of the study (IRB ID # - 20021004).

Patients who underwent EVT for AIS from January 2015 to 2020 were identified through a prospectively maintained stroke registry of all hospitalized patients with the diagnosis of AIS. We (KJ, PG) manually screened this registry for patients who underwent EVT. We then did a thorough chart search on our electronic medical records system Epic (Epic Systems, Verona, WI), using keywords 'Cancer', 'Malignancy' and 'Metastasis' to identify patients with cancer. These charts were further reviewed to confirm cancer with a positive histopathology report from previous biopsy/resection and the consulting oncologist's note. Patients were divided into two groups based on the presence or absence of cancer. All patients who were diagnosed with cancer and were either receiving treatment (surgery, radiation therapy and/or chemotherapy) or were treated conservatively, or those who were diagnosed with but refused treatment for cancer, were included in the cancer cohort. We collected information on the type of cancer, cancer staging, pathology, and treatment.

A propensity score match, as described by Rubin *et al*,[7] was performed between EVT + cancer patients and those without cancer[7 8] (EVT only). We matched numeric baseline modified Rankin Scale (mRS), numeric age and sex with a matching ratio of 1:5. We used exact mRS and age to assign propensity scores.

Acute stroke imaging and thrombectomy techniques

All AIS patients were screened on admission by a vascular neurologist who performed NIHSS and mRS assessments. Baseline imaging included a non-contrast head CT and CT angiography of the head and neck with or without perfusion. Patients received IV-tPA and/or underwent EVT based on the currently published American Heart Association/American Stroke Association guidelines.[9] Head CT or MRI of the brain were obtained within 24 hours post-intervention. Stroke etiology was classified according to the Trial of ORG 10,172 in Acute Stroke Treatment (TOAST) criteria.[10] Stent retriever thrombectomy and contact aspiration thrombectomy alone or in combination were used to perform the thrombectomy procedure.

Outcome measures

The severity of 90-day disability was assessed according to the distribution of scores across the mRS (shift analysis) as primary outcome. Self-reported reperfusion grade was evaluated according to the modified Thrombolysis In Cerebral Infarction (mTICI) scale, with successful reperfusion defined as a score ≥2b.[11] Intracerebral hemorrhage included any subarachnoid or intraparenchymal hemorrhage found on follow-up imaging and was classified according to the Heidelberg Bleeding Classification.[12]

Statistical analysis

Patient characteristics were compared with two-sample t-test or Wilcoxon rank sum test for continuous variables, and χ^2 test for categorical variables. Logistic regression was used to evaluate the association between hemorrhagic transformation (HT) and IV-tPA in the two cohort groups. Change in mRS from baseline to 3 months within cases were tested with Wilcoxon signed rank test. Characteristics of cancer patients including type of primary cancer, location, and staging were compared between TICI score groups (TICI 2b/3 vs other), mRS groups (0–2 vs 3–6 at 3 months), and HT groups (yes or no) with χ^2 test or Fisher's exact test (for categorical variables) and two-sample t-test (for continuous variables).

RESULTS

Baseline characteristics

Between January 2015 and 2020, 380 patients underwent EVT and 19 patients had active cancer at the time of the procedure. Mean age was 70.89±11.16 years, and 89.47% were women (n=17). In the propensity matched cohort, there were 95 patients in the control (EVT only) group, matched for age (71±11 years), sex (89% female) and baseline mRS (0–36.8%, 1–42.1%, and 2–21.1%).

Lung cancer was the most common malignancy (31.57%, n=6), followed by breast cancer (15.79%, n=3). Other malignancies included gastrointestinal, hematological, hepatobiliary, prostate and urogenital. Six patients (40%) had stage 4 cancer (table 1). Stroke etiology was cardioembolic in four (21.05%) patients, cancer-associated coagulopathy in eight (42%), underlying cardioembolism in four (21.05%), and undetermined in three (15.9%) patients.

Table 1 Descriptive statistics of the cases with active cancer

Demographics	N = 19
Age, mean±SD	71±11.6
Sex, n (%)	
Female	17 (89)
Male	2 (10.5)
Race, n (%)	
African American	5 (27.8)
Caucasian	9 (50.0)
Hispanic	2 (11.1)
Other	2 (11.1)
Missing	1
Hemorrhagic transformation, n (%)	
PH3c	2 (10.5)
HI1	5 (26.3)
PH1	3 (15.8)
PH2	1 (5.3)
No	8 (42.1)
Discharge disposition, n (%)	11 (57.9)
Acute rehabilitation	1 (5.3)
Home	4 (21.0)
Hospice	3 (15.8)
Dead	1 (5.3)
Patient alive at end of 1 year, n (%)	9 (60.0)
Missing	4
Able to continue cancer treatment after thrombectomy, n (%)	7 (47)
Missing	4
Location and type of primary tumor and metastasis, n (%)	
Breast cancer	3 (15.8)
Gastrointestinal	2 (10.5)
Hematological	2 (10.5)
Hepatobiliary	1 (5.3)
Lung adenocarcinoma	5 (26.3)
Small cell carcinoma of lung	1 (5.3)
Prostate cancer	1 (5.3)
Urogenital	4 (21.1)

HI, hemorrhagic infarction; PH, parenchymal hematoma.

Clinical, radiographic and angiographic characteristics

Cancer cohort

The middle cerebral artery was occluded most often (74%, n=14) followed by the internal carotid artery terminus (26%, n=2). Sixteen of 19 (84%) had a pre-procedural mRS of 0–1, and mean initial NIHSS score was 22±7.5. Eight of 19 (42%) received IV-tPA. TICI 2b/3 was achieved in 89.5% (n=17) patients. HT occurred in 11/19 (58%) patients. Discharge disposition was to an acute rehabilitation unit in 11 (58%) patients, home in four (21%), and hospice in three (15.8%). One patient (5%) died during hospitalization. Of the nine patients who were seen at 3 months follow-up, nine patients (60%) were alive at the end of 1 year, of whom seven (47%) were continuing cancer treatment (table 1).

Table 2 Comparison of cases with active cancer and controls after propensity matching

Characteristics	Control, N=95	Case, N=19	P value
Age, mean±SD	70.7±11.4	70.9±11.16	0.94
Sex, n (%)			1
Female	85 (89.5)	17 (89.5)	
Male	10 (10.5)	2 (10.5)	
Baseline mRS, n (%)			1
0	35 (36.8)	7 (36.8)	
1	40 (42.1)	9 (47.4)	
2	20 (21.1)	3 (15.8)	
Initial NIHSS, median (IQR)	22 (9.5)	22 (7.5)	0
Location of occlusion, n (%)			0
ICA terminus	19 (20%)	5 (26.3)	
Tandem occlusion	8 (0.08%)	1 (5.3)	
MCA	68 (71.5%)	14 (73.7)	
TICI 2b/3 recanalization	87 (91.5)	17 (89.5)	0.88
mRS at 3 months, n (%)			0.54
0	18 (18.9)	1 (6.7)	
1	14 (14.7)	4 (26.7)	
2	11 (11.6)	2 (13.3)	
3	15 (15.8)	1 (6.7)	
4	10 (10.5)	1 (6.7)	
5	6 (6.3)	0 (0.0)	
6	21 (22.1)	6 (40.0)	
Median (IQR)	3 (4)	3 (5)	0
Missing	0	4	
Survival at 3 months, n (%)			0
Alive	74 (77.9)	9 (60)	
Dead	21 (22.1)	6 (40)	
Missing	0	4	
NIHSS change, median (IQR)	−11 (10)	−7 (10.5)	0.3
Missing	20	0	
Hemorrhagic transformation, n (%)	5 (6.5)	11 (57.9)	<0.001
Missing	18	0	

ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis In Cerebral Infarction.

Table 3 Comparison of patients with or without hemorrhagic transformation in the active cancer group

	Yes	No	
Hemorrhagic transformation	N=11	N=8	P value
Location/type of primary tumor, n (%)			0.75
Breast cancer	2 (18)	1 (12.5)	
Gastrointestinal	1 (9)	1 (12.5)	
Hematological	2 (18)	0	
Hepatobiliary	1 (9)	0	
Lung adenocarcinoma	2 (18)	3 (37.5)	
Prostate cancer	1 (9.1)	0	
Urogenital	1 (9)	3 (37.5)	
Small cell carcinoma of the lung	1 (9)	0	
Stage of primary tumor, n (%)			1
I	1 (12.5)	0	
II	2 (25.0)	1 (12.5)	
III	3 (37.5)	3 (37.5)	
IV	2 (25.0)	4 (50.0)	
Missing	3	0	
Anticoagulants—yes, n (%)	2 (20)	3 (37.5)	0.61
Missing	1		
Last known well (hours), mean±SD	4.50±1.48	3.96±1.7	0
ASPECTS, median (IQR)	7.5 (2.8)	8 (2.3)	
Missing	1		
IV-tPA, n (%)	7 (63.6)	1 (12.5)	0

ASPECTS, Alberta Stroke Program Early CT Score; IV-tPA, intravenous tissue plasminogen activator.

Comparison between patients with cancer and propensity matched cohort

There were no statistically significant differences in recanalization rates, 90-day mRS, mortality or change in NIHSS score at 3 months (table 2) between the two groups. The number of patients with favorable mRS (0–2) in the non-cancer group was 45.2% compared with 46.7% in the cancer group, which was statistically non-significant (p=0.54). Seventy-four (77%) patients in the non-cancer group and nine (60%) patients in the cancer group were alive at 3 months. We measured the NIHSS change from discharge to NIHSS at 3 months. There was mean improvement of 11 points (IQR 10) in the non-cancer group and improvement of 7 points (IQR 10.5) in the cancer group, which was statistically comparable (p=0.3). Logistic regression was performed comparing HT in the control group and patients with cancer, with significantly higher HT in the cancer group (OR 41.3, 95% CI 9.13 to 307.83; p<0.001). None of the patients with HT were symptomatic in either group.

Sub-group analysis in patients with hemorrhagic transformation

Of the 11 patients in the cancer group with HT, there was no significant difference in the type or stage of cancer. In the cancer cohort, two (20%) patients were on anticoagulation and three (37.5%) patients were not (20% vs 37.5%, p=0.61). Seven (63.64%) patients in the HT and one (12.5%) patient in the non-HT had received IV-tPA (63.64% vs 12.50%, p=0.06) (table 3).

Factors associated with unfavorable outcomes

Favorable outcomes (mRS 0–3) did not differ between the two groups based on type and location of tumor. mRS at 3 months was available for 15/19 patients with mRS 0–3 in eight and mRS >3 in seven patients. More than half of those with mRS >3 had advanced stage IV cancer as compared with only 25% of those with mRS 0–3. No statistically significant difference in outcome was found in patients with prior anticoagulant use (12.5% vs 16.67%, p=1), last known well (mean LKW 4.26 vs 4.11 hours) or use of IV-tPA (4/8 (50%) vs 3/7 (42.8%), p=1) in the favorable versus unfavorable groups, respectively. Similarly, anticoagulant use on presentation (12.5% vs 16.7%, p=1), ASPECTS score (7.5 (IQR 1.5) vs 9 (IQR 1.5), p=0.39), or IV-tPA use (4/8 (50%) vs 3/7 (42%), p=1) were not statistically different in the mRS 0–3 or mRS >3 groups, respectively.

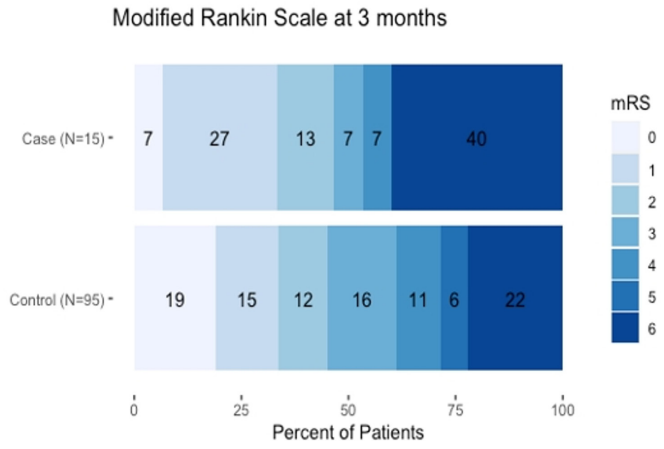

Figure 1 Scores on the modified Rankin Scale (mRS) at 3 months.

DISCUSSION

Our single center propensity-matched study characterized patients with cancer who underwent thrombectomy and analyzed radiographic and clinical outcomes. Patients with cancer tended to be older and female. The majority had a suspected cancer-associated coagulopathy while the next most frequent etiology was an underlying cardioembolic source. Successful recanalization (TICI 2b/3) was achieved in the majority of the patients. Despite a higher rate of HT compared with controls, 78.9% of patients with cancer were discharged to either home or to acute rehabilitation and had a discharge mRS ≤2 (figure 1).

Cerebrovascular disease has been reported to occur at a rate of 6.9% within the first year of cancer diagnosis.[13] Most cancer patients with stroke have known metastases, although patients with early-stage cancers can also develop stroke.[14] Historically, trials for thrombolysis and endovascular thrombectomy excluded patients with cancer out of concern for clinical futility and a higher hemorrhagic risk.[15 16] Though our study did show a higher HT risk among cancer patients, clinical outcomes at the time of discharge were similar.

Cancer-associated coagulopathy is an important risk factor for ischemic stroke within the first 6 months of the diagnosis (hazard ratio of 1.8 for a 6-month cumulative incidence of AIS),[13] particularly in patients with advanced stage adenocarcinoma, and is associated with unfavorable outcomes. Adenocarcinomas secrete mucins which activate platelets via P-selectin and L-selectin.[17] The subsequent pro-coagulant activity can lead to embolism. Given the higher incidence of both arterial and venous thrombosis in these patients, most patients are prophylactically placed on antiplatelets or anticoagulants which could theoretically portend a higher post-procedural hemorrhagic risk. In our series 5/19 (26.3%) patients with cancer were taking anticoagulants. On sub-group analysis, 2/11 (20.5%) patients with HT were taking anticoagulants and 3/8 (37.5%) were not taking anticoagulants. Though this does appear clinically significant, it did not achieve statistical significance (p=0.61).

In our study, three (15.8%) cancer patients died during the index hospitalization and these deaths were related to the stroke and not cancer. At the end of 1 year, nine (60%) of the 15 patients for whom data were available were alive. Of these nine patients, seven (47%) were able to continue with cancer treatment. Lee *et al* reported a series of 26 patients with cancer who underwent thrombectomy.[18] They noted a 90-day mortality rate of 30.8% (8/26) and, in addition, stroke-related deaths were more common than cancer-related deaths in the cancer group, which was similar to our observations. Discontinuation of anti-cancer therapy could be a potential cause for long-term mortality in these patients and potentially contribute to the concern for poor outcome in these patients.[1] In our series, almost half of the patients who underwent EVT could actually continue their cancer treatment.

Our study had several limitations, with its retrospective study design, limited sample size and sampling from a single comprehensive stroke center. The actual number of patients who underwent EVT may have been limited by selection bias due to concerns about cancer prognosis. False negatives are possible as well in the control group as some may have had occult cancer. We did not consider a detailed analysis of the stage of cancer or treatment, which along with the type of cancer could influence outcomes. Lastly, thrombus analysis to potentially determine the underlying etiology of the large vessel occlusion was not performed.

Cancer is a very heterogeneous entity and is also becoming increasingly prevalent in an aging population. A granular analysis of the effect of each specific type and stage of cancer on thrombectomy outcomes may be impractical because such information is often not available to the neurointerventionalist who is quickly triaging a potential stroke thrombectomy candidate. Furthermore, our operational classification of cancer is not only consistent with prior published studies, but does provide additional detail. Even though our study appears to have only a small number of patients with cancer, propensity matching analysis allowed us to measure the potential effect of cancer more clearly on stroke outcomes.

CONCLUSION

In this propensity matched analysis, we noted no significant difference in 90-day functional outcomes and mortality in patients undergoing endovascular therapy for acute ischemic stroke with and without active cancer. Our results suggest that in patients with acute large vessel occlusions, active cancer does not confer either radiographic and/or clinical futility. However, significantly higher rates of HT were found. Additional analysis of the implications of the type and cancer staging may provide further insight.

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Contributors KCJ, PG and AB-F were involved in conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafting the work or revising it critically for important intellectual content; AND Final approval of the version to be published. AV, NO and RD were involved in drafting the work or revising it critically for important intellectual content; AND final approval of the version to be published. MC made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafting the work or revising it critically for important intellectual content; AND final approval of the version to be published. KJ, PG and MC are guarantors of the overall content. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1 Lee E-J, Bae J, Jeong H-B, *et al*. Effectiveness of mechanical thrombectomy in cancer-related stroke and associated factors with unfavorable outcome. *BMC Neurol* 2021;21:1–10.
2 Rinaldo L, Cloft HJ, Rangel Castilla L, *et al*. Utilization rates of tissue plasminogen activator and mechanical thrombectomy in patients with acute stroke and underlying malignancy. *J Neurointerv Surg* 2019;11:768–71.
3 Benjamin EJ, Virani SS, Callaway CW, *et al*. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation* 2018;137:e67–492.
4 Bang OY, Seok JM, Kim SG, *et al*. Ischemic stroke and cancer: stroke severely impacts cancer patients, while cancer increases the number of strokes. *J Clin Neurol* 2011;7:53.
5 Gallo A, Galliazzo S, Grazioli S, *et al*. Epidemiology and secondary prevention of ischemic stroke in patients on antiplatelet drug: a retrospective cohort study. *J Thromb Thrombolysis* 2019;48:336–44.
6 Zuo P-Y, Chen X-L, Liu Y-W, *et al*. Increased risk of cerebrovascular events in patients with cancer treated with bevacizumab: a meta-analysis. *PLoS One* 2014;9:e102484.
7 Rubin DB. Using propensity scores to help design observational studies: application to the tobacco litigation. *Health Services and Outcomes Research Methodology* 2001;2:169–88.
8 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107.
9 Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019;50:e344–418.
10 Fure B, Wyller TB, Thommessen B. TOAST criteria applied in acute ischemic stroke. *Acta Neurol Scand* 2005;112:254–8.
11 Fugate JE, Klunder AM, Kallmes DF. What Is meant by "TICI"? *AJNR Am J Neuroradiol* 2013;34:1792–7.
12 Neuberger U, Möhlenbruch MA, Herweh C, *et al*. Classification of bleeding events: comparison of ECASS III (European Cooperative Acute Stroke Study) and the new Heidelberg bleeding classification. *Stroke* 2017;48:1983–5.
13 Navi BB, Reiner AS, Kamel H, *et al*. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol* 2017;70:926–38.
14 Sporns PB, Krähling H, Psychogios MN, *et al*. Small thrombus size, thrombus composition, and poor collaterals predict pre-interventional thrombus migration. *J Neurointerv Surg* 2021;13:409–14.
15 Goyal M, Menon BK, van Zwam WH, *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
16 Nogueira RG, Jadhav AP, Haussen DC, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;378:11–21.
17 Wahrenbrock M, Borsig L, Le D, *et al*. Selectin-mucin interactions as a probable molecular explanation for the association of Trousseau syndrome with mucinous adenocarcinomas. *J Clin Invest* 2003;112:853–62.
18 Lee D, Lee DH, Suh DC, *et al*. Intra-arterial thrombectomy for acute ischaemic stroke patients with active cancer. *J Neurol* 2019;266:2286–93.