Clinical outcome after endovascular treatment in patients with active cancer and ischemic stroke: a MR CLEAN registry substudy

Verschoof, M.A.; Groot, A.E.; Bruijn, S.F.T.M. de; Roozenbeek, B.; Worp, H.B. van der; Dippel, D.W.J.; ... ; MR CLEAN Registry Investigators

RESEARCH ARTICLE

Clinical Outcome After Endovascular Treatment in Patients With Active Cancer and Ischemic Stroke

A MR CLEAN Registry Substudy

Merelijne A. Verschoof, MD, Adrien E. Groot, MD, PhD, Sebastiaan F.T.M. de Bruijn, MD, PhD, Bob Roozenbeek, MD, PhD, H. Bart van der Worp, MD, PhD, Diederik W.J. Dippel, MD, PhD, Bart J. Emmer, MD, PhD, Stefan D. Roosendaal, MD, PhD, Charles B.L.M. Majoie, MD, PhD, Yvo B.W.E.M. Roos, MD, PhD, and Jonathan M. Coutinho, MD, PhD, on behalf of the MR CLEAN Registry Investigators

Correspondence
Dr. Coutinho
j.coutinho@amsterdamumc.nl

Neurology® 2022;98:e993-e1001. doi:10.1212/WNL.0000000000013316

Abstract

Background and Objectives

To explore clinical and safety outcomes of patients with acute ischemic stroke (AIS) and active cancer after endovascular treatment (EVT).

Methods

Using data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry, we compared patients with active cancer (defined as cancer diagnosed within 12 months before stroke, metastatic disease, or current cancer treatment) to patients without cancer. Outcomes were 90-day modified Rankin Scale (mRS) score, mortality, successful reperfusion (expanded Treatment in Cerebral Infarction score ≥2b), symptomatic intracranial hemorrhage (sICH), and recurrent stroke. Subgroup analyses were performed in patients with a prestroke mRS score of 0 or 1 and according to treatment setting (curative or palliative). Analyses were adjusted for prognostic variables.

Results

Of 2,583 patients who underwent EVT, 124 (4.8%) had active cancer. They more often had prestroke disability (mRS score ≥2: 34.1% vs 16.6%). The treatment setting was palliative in 25.3% of the patients. There was a shift toward worse functional outcome at 90 days in patients with active cancer (adjusted common odds ratio [acOR] 2.2, 95% confidence interval [CI] 1.5–3.2). At 90 days, patients with active cancer were less often independent (mRS score 0–2: 22.6% vs 42.0%, adjusted OR [aOR] 0.5, 95% CI 0.3–0.8) and more often dead (52.2% vs 26.5%, aOR 3.2, 95% CI 2.1–4.9). Successful reperfusion (67.8% vs 60.5%, aOR 1.4, 95% CI 1.0–2.1) and sICH rates (6.5% vs 5.9%, aOR 1.1, 95% CI 0.5–2.3) did not differ. Recurrent stroke within 90 days was more common in patients with active cancer (4.0% vs 1.3%, aOR 3.1, 95% CI 1.2–8.1). The sensitivity analysis of patients with a prestroke mRS score of 0 or 1 showed that patients with active cancer still had a worse outcome at 90 days (acOR 1.9, 95% CI 1.2–3.0). Patients with active cancer in a palliative treatment setting regained functional independence less often compared to patients in a curative setting (18.2% vs 32.1%), and mortality was higher (81.8% vs 39.3%).

Discussion

Despite similar technical success, patients with active cancer had significantly worse outcomes after EVT for AIS. Moreover, they had an increased risk of recurrent stroke. Nevertheless, about a quarter of the patients regained functional independence, and the risk of other complications, most notably sICH, was not increased.

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

From Neurology (M.A.V., S.F.T.M.d.B.), HagaZiekenhuis, Den Haag; Neurology (A.E.G., Y.B.W.E.M.R., J.M.C.) and Radiology and Nuclear Medicine (B.J.E., S.D.R., C.B.L.M.M.), Amsterdam UMC, University of Amsterdam; Neurology (B.R., D.W.J.D.), Erasmus MC, Rotterdam; and Neurology and Neurosurgery (H.B.v.d.W.), UMC Utrecht, the Netherlands.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

MR CLEAN Registry Investigators are listed in Appendix 2 at links.lww.com/WNL/B758

Glossary

acOR = adjusted common odds ratio; **AIS** = acute ischemic stroke; **aOR** = adjusted odds ratio; **CI** = confidence interval; **EVT** = endovascular treatment; **IVT** = IV thrombolysis; **MR CLEAN** = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **sICH** = symptomatic intracranial hemorrhage.

Classification of Evidence

This study provides Class I evidence that patients with active cancer undergoing EVT for AIS have worse functional outcomes at 90 days compared to those without active cancer.

Patients with cancer are at increased risk of acute ischemic stroke (AIS), especially in the first months after diagnosis.[1,2] The stroke risk varies by cancer type and is generally higher in more advanced stages of the disease and in patients with adenocarcinomas.[3,4] About 10% of patients hospitalized with AIS are known to have cancer,[5,6] and 3% to 5% of patients are diagnosed with cancer within 2 years after stroke.[7] The most frequent types of cancer in patients with AIS are comparable to those in the general population, namely lung, gastrointestinal tract, and breast cancer.[8-11]

Previous studies have found that comorbid cancer is associated with increased stroke severity, stroke progression, and poor functional outcome.[11,12] In addition, the risk of stroke recurrence is 2- to 3-fold higher in these patients compared to patients without cancer.[8-10] Endovascular treatment (EVT) is often the only possible treatment modality in patients with AIS because patients with cancer regularly have contraindications for IV thrombolysis (IVT) such as recent surgery or coagulopathy.[11,13] However, except for case series and small-scale single-center studies, there are very few data on the short- and long-term outcomes after EVT in patients with stroke with cancer.[14-18]

The aim of our study was to compare the clinical, imaging, and safety outcomes of patients with AIS and active cancer who underwent EVT to those of patients without cancer.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

We used data from the Multicenter Randomized Clinical *Trial* of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry, a prospective, observational cohort study of consecutive patients with ischemic stroke undergoing EVT in the Netherlands.[19] This registry started immediately after the final randomization in March 2014 for the MR CLEAN trial.[20] The 17 intervention centers that participated in the MR CLEAN trial prospectively collected data from consecutive patients with AIS treated with EVT.

The medical ethics committee of the Erasmus University Medical Center in Rotterdam, the Netherlands approved the MR CLEAN Registry (MEC-2014-235). The research protocol was approved by the institutional review board of each participating center. The research boards waived the necessity of written informed consent.

Patients and Clinical Data

We included patients ≥18 years of age who were treated in a center that participated in the MR CLEAN trial with AIS of the anterior circulation for whom data on cancer status could be obtained from the discharge letters. Baseline characteristics, risk factors for stroke, imaging findings, and clinical outcomes were recorded with a standardized case record form. We distinguished 2 groups: patients with active cancer and patients without a history of cancer. Active cancer was defined as cancer diagnosis within 12 months before stroke, metastatic disease, or cancer treatment in the last 30 days. Patients who had declined cancer treatment were also considered to have active cancer. Patients with a history of cancer but not fulfilling the definition of active cancer were excluded from both groups. Noninvasive skin cancer (e.g., basal cell carcinoma), meningioma, myelodysplastic syndrome, and nonactive cancer diagnosed >10 years before stroke were not registered as (history of) cancer. For patients with active cancer, the date of diagnosis, type of cancer, and details of treatment were extracted from the medical records.

Data Availability

Under Dutch law, source data cannot be made available because no patient approval was obtained for sharing (coded) individual data. However, on reasonable request to the corresponding author, detailed syntax and output files of statistical analyses will be made available.

Outcome Measures

The primary outcome was functional outcome at 90 days, measured with the modified Rankin Scale (mRS). The mRS is a 7-point scale that ranges from 0 (no symptoms) to 6 (death).[21] Secondary outcomes were functional independence (defined as mRS score 0–2), mortality at 90 days, in-hospital mortality, NIH Stroke Scale (NIHSS) score at 24 to 48 hours, successful reperfusion (expanded Treatment in Cerebral Infarction scores

≥2b), symptomatic intracranial hemorrhage (sICH; defined as a decline in NIHSS score of ≥4 points and corresponding hemorrhage confirmed on imaging), recurrent stroke (defined as imaging of new brain infarction with corresponding clinical neurologic deficit), major extracranial bleeding (defined as any major bleeding as judged by local investigator), cardiac ischemia (defined as confirmed by ECG and release of appropriate biomarkers), and pneumonia (defined as an infection according to the Centers for Disease Control and Prevention *National Healthcare Safety Network* surveillance definition occurring within 7 days after the onset of stroke).[22]

Statistical Analysis

Intergroup comparisons were analyzed with the χ^2 test, independent *t* test or Mann-Whitney *U* test as appropriate. The cumulative probability of survival during the 90-day follow-up period was estimated with the Kaplan-Meier method. Intergroup comparison was performed with the log-rank test. For regression analyses, missing variables were imputed with multivariate imputation by chained equations with 5 imputations. We used multivariable ordinal, logistic, and linear regression analysis to calculate adjusted odds ratios (aORs) or adjusted common odds ratios (acORs) and β coefficients for all outcomes and adjusted for the following predefined prognostic factors: age, prestroke mRS score, baseline NIHSS score, and onset-to-door time. In an exploratory analysis, we additionally adjusted for IVT because patients with cancer more often have contraindications for IVT.

When no event occurred in 1 of the groups, we added 0.5 to all 4 cells of the 2 × 2 table for the unadjusted analyses.[23] We performed a subgroup analysis for the primary outcome including only data from patients with a prestroke mRS score of 0 or 1 and a descriptive analysis of patients with a prestroke mRS score of 3 to 5. We also performed a descriptive subgroup analysis according to treatment setting (curative or palliative) for functional independence and mortality. All analyses were performed with R software (version 3.4.2, R Foundation, Vienna, Austria).

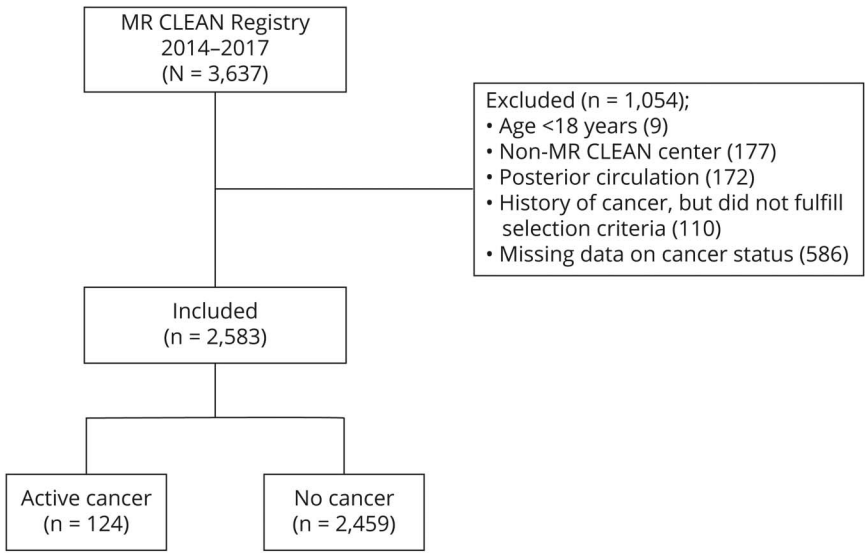
Results

Between 2014 and 2017, 3,380 patients with AIS received EVT in the Netherlands. Of these, 797 were excluded from the present study, mostly because data on cancer status were missing (Figure 1). Of the 2,583 patients who were included in the analysis, 124 (4.8%) had active cancer. The most common types of cancer were digestive tract (31.1%) and lung cancer (25.0%) cancer, and 73.1% had metastatic disease (Table 1). In total, 84.8% of patients with active cancer had received cancer treatment in the last 30 days, including chemotherapy (22.2%), radiation therapy (15.2%), surgery (13.4%), or a combination of therapies (31.3%). The treatment setting was palliative in 25.3% of the patients.

Baseline Characteristics

Mean age and sex ratios were similar in both groups (Table 2). Patients with active cancer more often had prestroke functional disability (prestroke mRS score ≥2: 34.1% vs 16.6%, $p < 0.001$). Stroke severity was similar in patients with active cancer compared to patients without cancer (both median NIHSS score 16). Patients with active cancer more often used therapeutic anticoagulation (31.5% vs 17.6%, $p < 0.001$) and less often received IVT (56.6% vs 75.8%, $p < 0.001$). General anesthesia during EVT was applied more often in patients with active cancer (31.9% vs 21.1%, $p = 0.005$). Workflow times were comparable.

Figure 1 Flowchart Patient Selection



MR CLEAN = Multicenter Randomized Clinical *Trial* of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands.

Table 1 Details of 124 Patients With Active Cancer

Type of cancer	No. (%)
Digestive tract	41/124 (33.1)
Lung	31/124 (25.0)
Urogenital	17/124 (13.7)
Breast	16/124 (12.9)
Gynecologic	9/124 (7.3)
Hematologic	3/124 (2.4)
Melanoma	3/124 (2.4)
Other[a]	4/124 (3.2)
Metastatic disease	
Yes	68/93 (73.1)
No	25/93 (26.9)
Treatment in last 30 d	
Chemotherapy	25/112 (22.2)
Radiation therapy	17/112 (15.2)
Surgery	15/112 (13.4)
Combination[b]	35/112 (31.3)
Other treatment	3/112 (2.7)
No current treatment	17/112 (13.7)
Treatment setting	
Curative	65/87 (74.7)
Palliative	22/87 (25.3)

[a] Metastases from unknown primary tumor (n = 2), malignant tumor lower leg (histopathologic findings not reported), and sarcoma central pulmonary artery.
[b] Chemoradiation therapy (n = 14), chemotherapy and surgery (n = 12), radiation therapy and surgery (n = 6), and chemoradiation therapy and surgery (n = 3).

Outcomes

Patients with active cancer had worse functional outcome at 90 days compared to those without cancer (acOR for a shift on mRS score toward worse outcome 2.2, 95% confidence interval [CI] 1.5–3.2, Figure 2). The frequency of functional independence at 90 days was lower (22.6% vs 42.0%, aOR 0.5, 95% CI 0.3–0.8) and the mortality was higher (52.2% vs 26.5%, aOR 3.2, 95% CI 2.1–4.9, Table 3 and Figure 3) in patients with active cancer. The in-hospital mortality was also higher in patients with active cancer (25.2% vs 15.2%, aOR 2.1, 95% CI 1.3–3.2). Successful reperfusion (67.8% vs 60.5%, aOR 1.4, 95% CI 1.0–2.1), median NIHSS score at 24 to 48 hours (12 vs 10, β coefficient 0.02, 95% CI −0.8 to 2.3), and sICH rates (6.5% vs 5.9%, aOR 1.1, 95% CI 0.5–2.3) did not differ between groups. Recurrent stroke within 90 days was ≈3 times more common in patients with active cancer (4.0% vs 1.3%, aOR 3.1, 95% CI 1.2–8.1). The risk of other complications was comparable between patients with active cancer and those without cancer. Additionally adjusting the multivariable analyses for IVT had no material effect on the strength of the association between cancer and outcome (acOR for a shift on the mRS toward worse outcome at 90 days 2.1, 95% CI 1.5–3.1, aOR for functional independence at 90 days 0.5, 95% CI 0.3–0.8, and aOR for mortality at 90 days 3.2, 95% CI 2.1–4.8).

In the sensitivity analysis using only data from patients with a prestroke mRS score of 0 or 1, patients with active cancer still had a worse outcome at 90 days (acOR 1.9, 95% CI 1.2–3.0, eFigure 1a, available from Zenodo, doi.org/10.5281/zenodo.5813275). For the subgroup of patients with a prestroke mRS score of 3 to 5, similar results were seen in patients with active cancer compared to patients without cancer (functional independence 3.8% vs 10.0% and mortality 65.4% vs 54.1%, eFigure 1b, available from Dryad.) The subgroup analyses according to treatment setting showed that patients with active cancer in a palliative treatment setting regained functional independence less often compared to patients in a curative setting (18.2% vs 32.1%) and that mortality was also higher (81.8% vs 39.3%).

This study provides Class I evidence that patients with active cancer undergoing EVT for AIS have worse functional outcomes at 90 days compared to those without active cancer.

Discussion

Comorbid active cancer was associated with a worse functional outcome and increased mortality in patients with AIS who received EVT compared to patients without cancer. Approximately half of the patients with active cancer died within 90 days after undergoing EVT, and among patients who were in a palliative setting, this proportion increased to 80%. The risk of recurrent stroke was also 3 times higher in patients with active cancer. The association between active cancer and poor outcome persisted in patients who had no prestroke disability. Still, a quarter of the patients with active cancer regained functional independence at 90 days, and other complication rates, most notably sICH, were not increased in patients with active cancer.

Our results are in line with 3 smaller previous studies focusing on patients with cancer with AIS treated with EVT, with good functional outcome rates between 15% and 36% and mortality between 30% and 60%, despite achieving successful reperfusion in 63% to 89% of cases.[16-18] None of these studies reported recurrent stroke, but other studies on AIS in patients with cancer found an increased risk similar to that in the present study.[8-10]

A number of factors may explain the increased risk of stroke in patients with cancer.[1,2] First, cancer may cause hypercoagulability, for example, due to increased levels of procoagulant factors and tumor-secreted microparticles triggering thrombosis.[24,25] Second, cancer and stroke share risk factors, in particular smoking and obesity.[2,3,26] Third, chemotherapy may enhance thrombin generation; radiotherapy may cause vasculopathy; and

Table 2 Baseline Characteristics

	Active cancer (n = 124)	No cancer (n = 2,459)	*p* Value
Age, mean ± SD, y	69 ± 11	70 ± 14	0.660
Male sex, n (%)	58/124 (46.8)	1,277/2,459 (51.9)	0.262
Prestroke mRS score, n (%)			<0.001
0	64/123 (52.0)	1712/2,421 (70.7)	
1	17/123 (13.8)	307/2,421 (12.7)	
2	16/123 (13.0)	162/2,421 (6.7)	
3	13/123 (10.6)	141/2,421 (5.8)	
4	11/123 (8.9)	79/2,421 (3.3)	
5	2/123 (1.6)	20/2,421 (0.8)	
Prestroke mRS score ≥2, n (%)	42/123 (34.1)	402/2,421 (16.6)	<0.001
NIHSS score, median (IQR)[a]	16 (12–19)	16 (11–19)	0.275
Medical history, n (%)			
Hypertension	50/121 (41.3)	1,262/2,415 (52.3)	0.019
Previous stroke	17/122 (13.9)	408/2,445 (16.7)	0.425
Diabetes	25/122 (20.5)	391/2,446 (16.0)	0.187
Myocardial infarction	16/122 (13.1)	333/2,422 (13.7)	0.843
Atrial fibrillation	32/122 (26.2)	582/2,434 (23.9)	0.559
Hypercholesterolemia	32/120 (26.7)	696/2,360 (29.5)	0.507
Peripheral arterial disease	14/122 (11.5)	232/2,418 (9.6)	0.493
Smoking	36/121 (29.8)	531/2,441 (21.8)	0.001
Medication, n (%)			
Blood pressure medication	62/121 (51.2)	1,311/2,418 (54.2)	0.521
Statins	37/120 (30.8)	844/2,413 (35.0)	0.352
Therapeutic anticoagulation[b]	39/124 (31.5)	434/2,459 (17.6)	<0.001
Antiplatelet therapy	38/122 (31.1)	743/2,432 (30.6)	0.889
Mean ± SD blood pressure, mm Hg			
Systolic[c]	145 ± 25	150 ± 25	0.026
Diastolic[d]	80 ± 16	82 ± 16	0.164
Laboratory results, mean ± SD			
Glucose, mg/dL[e]	7.4 ± 2.5	7.5 ± 2.3	0.826
INR[f]	1.23 ± 0.40	1.18 ± 0.42	0.227
Thrombocyte count, n[g]	272 ± 120	249 ± 83	0.006
IVT, n (%)	69/123 (56.6)	1862/2,457 (75.8)	<0.001
Procedure, n (%)			
General anesthesia	38/119 (31.9)	490/2,324 (21.1)	0.005
Balloon guiding	59/86 (68.6)	1,227/1,848 (66.4)	0.671
EVT performed	110/124 (88.7)	2,083/2,459 (84.7)	0.608
Time, median (IQR), min			

Continued

Table 2 Baseline Characteristics *(continued)*

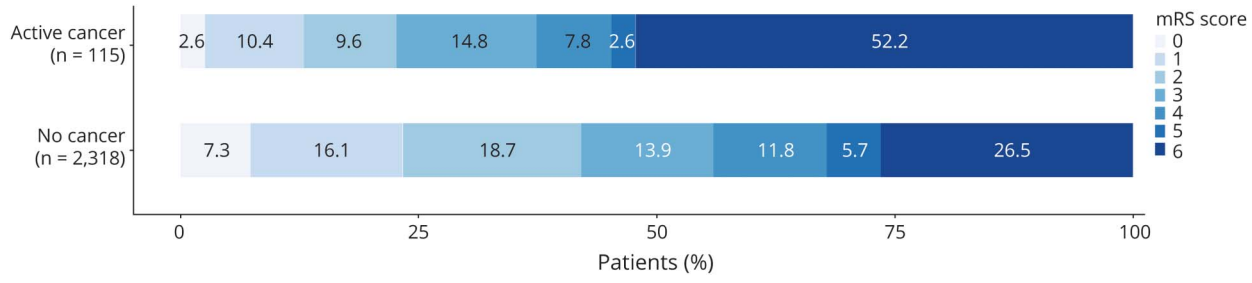
	Active cancer (n = 124)	No cancer (n = 2,459)	*p* Value
Onset to door[h]	64 (40–113)	57 (39–105)	0.296
Onset to groin[i]	203 (155–258)	200 (153–260)	0.897
Onset to reperfusion[j]	255 (203–335)	256 (204–320)	0.817
Door to needle[k]	25 (19–40)	24 (18–32)	0.199
Door to groin[l]	119 (85–152)	121 (88–157)	0.495
Duration of procedure[m]	56 (40–78)	60 (38–85)	0.717
ASPECTS, median (IQR)[n]	9 (8–10)	9 (7–10)	0.094
Occlusion location, n (%)			0.568
Intracranial ICA	5/117 (4.3)	130/2,348 (5.5)	
ICA-T	26/117 (22.2)	487/2,348 (20.7)	
M1	73/117 (62.4)	1,350/2,348 (57.5)	
M2	12/117 (10.3)	364/2,348 (15.5)	
Other[o]	1/117 (0.9)	17/2,348 (0.7)	

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; EVT = endovascular therapy; ICA = internal carotid artery; ICA-T = internal carotid artery terminus; INR = international normalized ratio; IQR= interquartile range; IVT = IV thrombolysis; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.
Number of missing values:[a]3 (2.4%) vs 26 (1.1%),[c]5 (4.0%) vs 33 (1.3%),[d]5 (4.0%) vs 41 (1.7%),[e]11 (8.9%) vs 284 (11.5%),[f]26 (21.0%) vs 451 (18.3%), [g]14 (11.3%) vs 339 (13.8%),[h]22 (17.7%) vs 398 (16.1%),[i]1 (0.8%) vs 8 (0.3%), [j]9 (7.3%) vs 144 (5.9%),[k]12 (9.7%) vs 364 (14.8%),[l]38 (30.6%) vs 551 (22.4%), [m]12 (9.7%) vs 210 8.5%), and [n]1 (0.8%) vs 81 (3.3%).
[b] Vitamin K antagonist (missing = 16), low-molecular-weight heparin (missing = 32), direct oral anticoagulant (missing = 34).
[o] M3, A1, or A2.

immune checkpoint inhibitors may cause cardiac events, which can also result in stroke.[27-29] Unfortunately, detailed information on use of immune checkpoint inhibitors was not available for the patients in our cohort.

Approximately 1 of every 4 patients with active cancer regained functional independence at 90 days after EVT. This percentage is only slightly higher than what was achieved in the (non-EVT) control arm of the MR CLEAN trial (19%).[20] It is also quite similar to the frequency of functional independence achieved by octogenarians after EVT.[30] Whether this proportion is considered to be worthwhile probably varies both among physicians and patients. On one hand, some would argue that a good outcome rate of one-quarter is insufficient to warrant an invasive and costly procedure such as EVT. On the other hand, one could also argue that this proportion is worth the effort of EVT, especially because the complication rate was not increased and because, if one refrains from EVT, the outcome of these patients is almost certainly invariably poor.[12] Our results cannot give a definitive answer on the efficacy and safety of EVT in the specific subgroup of patients with AIS and active cancer, but by providing detailed data, we hope that physicians and patients are better equipped to make an informed decision.

Figure 2 mRS Scores at 90 Days



Comparison of 90-day modified Rankin Scale (mRS) score in patients with active cancer (n = 115) vs no cancer (n = 2,318). There was a shift toward worse outcome for patients with active cancer (adjusted common odds ratio 2.17, 95% confidence interval 1.48–3.16).

Table 3 Outcomes After 90 Days

	Active cancer (n = 124)	No cancer,[e] (n = 2,459)	Unadjusted β/OR (95% CI)	Adjusted β/OR (95% CI)
mRS at 90 d, median (IQR)a	6 (3–6)	3 (2–6)	2.50 (1.76 to 3.54)	2.17 (1.48 to 3.16)[c]
Functional independence at 90 d (mRS score 0–2), n (%)	26/115 (22.6)	976/2,318 (42.1)	0.42 (0.27 to 0.65)	0.50 (0.31 to 0.81)[c]
Mortality at 90 d, n (%)	60/115 (52.2)	614/2,318 (26.5)	2.87 (1.96 to 4.17)	3.17 (2.07 to 4.85)[c]
In-hospital mortality, n (%)	29/115 (25.2)	353/2,318 (15.2)	2.03 (1.34 to 3.06)	2.05 (1.32 to 3.18)[c]
NIHSS score at 24–48 h, median (IQR)b	12 (5–18)	10 (4–17)	0.04 (−0.21 to 2.98)	0.02 (−0.75 to 2.32)[c]
eTICI score ≥2B, n (%)	82/121 (67.8)	1,451/2,397 (60.5)	1.35 (0.92 to 1.99)	1.40 (0.95 to 2.07)[c]
0	14/121 (11.6)	410/2,397 (17.1)		
1	3/121 (2.5)	78/2,397 (3.3)		
2A	22/121 (18.2)	458/2,397 (19.1)		
2B	27/121 (22.3)	518/2,397 (21.6)		
2C	18/121 (14.9)	251/2,397 (10.5)		
3	37/121 (30.6)	682/2,397 (28.5)		
sICH, n (%)	8/124 (6.5)	146/2,459 (5.9)	1.09 (0.52 to 2.28)	1.12 (0.53 to 2.34)[d]
Recurrent stroke, n (%)	5/124 (4.0)	33/2,459 (1.3)	3.10 (1.18 to 8.06)	3.06 (1.16 to 8.06)[d]
Extracranial hemorrhage, n (%)	4/124 (3.2)	48/2,459 (2.0)	1.68 (0.59 to 4.74)	1.54 (0.54 to 4.39)[d]
Pneumonia, n (%)	11/124 (8.9)	261/2,459 (10.7)	0.82 (0.44 to 1.54)	0.74 (0.39 to 1.40)[d]
Cardiac ischemia, n (%)	2/124 (1.6)	11/2,459 (0.4)	3.65 (0.80 to 16.67)	3.56 (0.77 to 16.67)[d]

Abbreviations: eTICI = expanded Treatment in Cerebral Infarction; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio; sICH = symptomatic intracranial hemorrhage.
Number of missing values:[a]9 (7.3%) vs 141 (5.7%) and [b]9 (7.3%) vs 200 (8.1%).
[c] Adjusted for age, prestroke mRS score, baseline NIHSS score, and onset-to-door time.
[d] Adjusted for baseline NIHSS score and anticoagulation.
[e] Reference category.

Our study has a number of limitations. First, the cause of death was not assessed in the MR CLEAN Registry, and it is therefore unknown whether patients with active cancer died of stroke-related or cancer-related causes. Other studies on cancer and AIS, not targeted at EVT, reported overall mortality similar to that in our study.[12,26] Two previous studies focusing on EVT in patients with cancer with AIS reported vascular disease as the cause of death in 5 of 12 (41.7%) and stroke-related death in 5 of 8 (62.5%), respectively.[16,17] Second, there might have been a bias in the selection of patients with cancer who received EVT. In some patients, local physicians may have decided to refrain from EVT because of a poor prognosis. Because the MR CLEAN Registry collects data of only patients who actually received EVT (not of patients who were potentially eligible for EVT), we cannot be certain how often this situation occurred. On the other hand, it is also possible that bias occurred after EVT. Patients with cancer who developed AIS might have decided not to have complications treated, not to undergo extensive stroke rehabilitation, or to cease treatment for cancer. This might have contributed to worse functional outcomes. Third, not all details about cancer status could be obtained. A more detailed database would have allowed us to further explore possible heterogeneity among patients with cancer.

Despite similar technical success, patients with active cancer had significantly worse outcomes after EVT for AIS, even when their prestroke functioning was favorable (mRS score 0–1). Moreover, they had an increased risk of recurrent stroke. Nevertheless, about a quarter of the patients regained functional independence, and the risk of other complications, most notably sICH, was not increased.

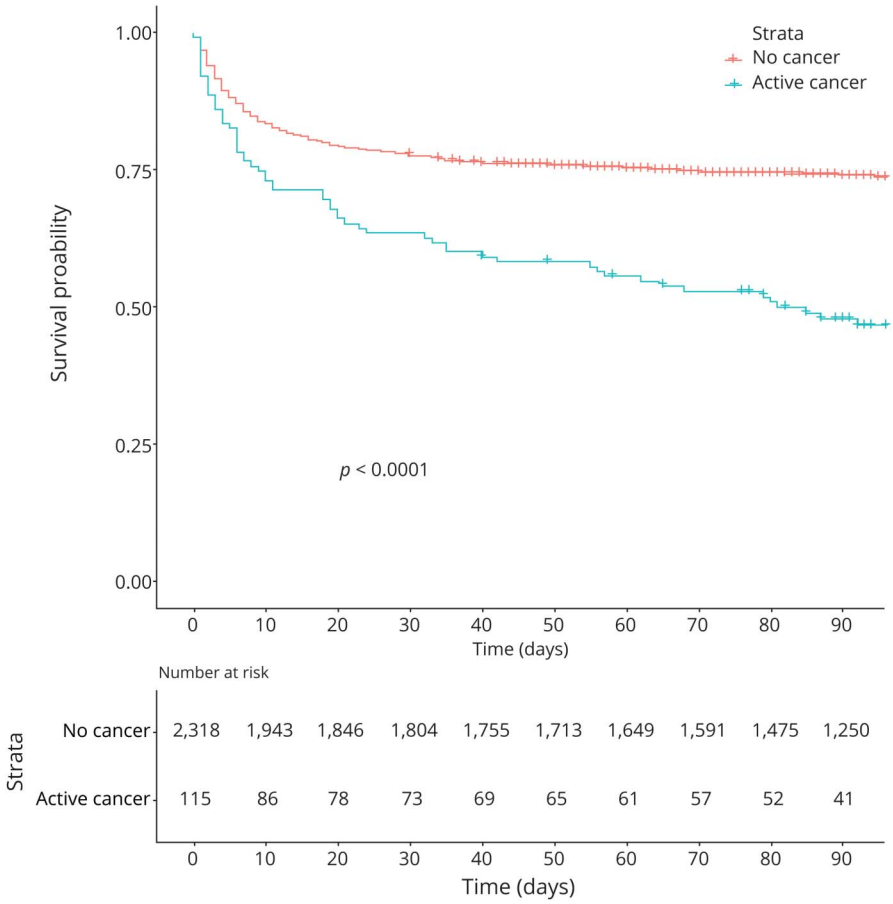
Study Funding

The MR CLEAN Registry was funded and carried out by Erasmus MC University Medical Center, Amsterdam UMC, and Maastricht University Medical Center. The MR CLEAN Registry was additionally funded by the TWIN Foundation.

Disclosure

B.J. Emmer reports funding from ZonMW (Leading the Change) and Health Holland paid to institution and has received grants paid

Figure 3 Kaplan-Meier Survival Curve of Cumulative Mortality During the 90-Day Follow-up Period in Patients With Active Cancer vs No Cancer



to institution from Stryker Neurovascular in the past and personal fees from Dekra and from Novartis outside the submitted work in the past. C.B.L.M. Majoie reports grants from CVON/Dutch Heart Foundation, European Commission, TWIN Foundation, Stryker, and Health Evaluation Netherlands, all outside the submitted work (paid to institution), and is shareholder of Nico. lab, a company that focuses on the use of artificial intelligence for medical image analysis. Y.B.W.E.M. Roos is a minor shareholder of Nico. lab. H.B. van der Worp has received speaker's fees Boehringer Ingelheim, has served as a consultant to Boehringer Ingelheim, and is the recipient of unrestricted grants from Dutch Heart Foundation and the European Union for the conduct of trials on acute treatment for stroke, all outside the submitted work. D.W.J. Dippel reports fees for consultations by Stryker and Bracco Imaging; grants from Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Research and Development, The Netherlands Organisation for Health Research and Development, and Health Holland Top Sector Life Sciences & Health; and unrestricted grants from AngioCare BV, Covidien/EV3, MEDAC Gmbh/LAMEPRO, Top Medical/Concentric, Stryker, Stryker European Operations BV, Penumbra Inc, Medtronic, Thrombolytic Science, LLC, and Cerenovus, all paid to institution. J.M. Coutinho received unrelated research support from the Dutch Heart Foundation, Bayer, Boehringer, and Medtronic. All fees were paid to his employer. All other authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* July 4, 2021. Accepted in final form December 28, 2021.

Appendix Authors

Name	Location	Contribution
Merelijne A. Verschoof, MD	Neurology, HagaZiekenhuis, Den Haag, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; Analysis or interpretation of data
Adrien E. Groot, MD, PhD	Neurology, Amsterdam UMC, University of Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

Appendix *(continued)*

Name	Location	Contribution
Sebastiaan F.T.M. de Bruijn, MD, PhD	Neurology, HagaZiekenhuis, Den Haag, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Bob Roozenbeek, MD, PhD, MD, PhD	Neurology, Erasmus MC, Rotterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
H. Bart van der Worp, MD, PhD	Neurology and Neurosurgery, UMC Utrecht, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Diederik W.J. Dippel, MD, PhD	Neurology, Erasmus MC, Rotterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Bart J. Emmer, MD, PhD	Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Stefan D. Roosendaal, MD, PhD	Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Charles B.L.M. Majoie, MD, PhD	Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Yvo B.W.E.M. Roos, MD, PhD	Neurology, Amsterdam UMC, University of Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Jonathan M. Coutinho, MD, PhD	Neurology, Amsterdam UMC, University of Amsterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B758

References

1. Navi BB, Reiner AS, Kamel H, et al. Association between incident cancer and subsequent stroke. *Ann Neurol.* 2015;77(2):291-300.
2. Zoller B, Ji J, Sundquist J, Sundquist K. Risk of haemorrhagic and ischaemic stroke in patients with cancer: a nationwide follow-up study from Sweden. *Eur J Cancer.* 2012;48(12):1875-1883.
3. Navi BB, Reiner AS, Kamel H, et al. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol.* 2017;70(8):926-938.
4. Kazmierczak M, Lewandowski K, Wojtukiewicz MZ, et al. Cancer procoagulant in patients with adenocarcinomas. *Blood Coagul Fibrinolysis.* 2005;16(8):543-547.
5. Sanossian N, Djabiras C, Mack WJ, Ovbiagele B. Trends in cancer diagnoses among inpatients hospitalized with stroke. *J Stroke Cerebrovasc Dis.* 2013;22(7):1146-1150.
6. Lindvig K, Moller H, Mosbech J, Jensen OM. The pattern of cancer in a large cohort of stroke patients. *Int J Epidemiol.* 1990;19(3):498-504.
7. Selvik HA, Thomassen L, Bjerkreim AT, Naess H. Cancer-associated stroke: the Bergen NORSTROKE study. *Cerebrovasc Dis Extra.* 2015;5(3):107-113.
8. Lau KK, Wong YK, Teo KC, et al. Stroke patients with a past history of cancer are at increased risk of recurrent stroke and cardiovascular mortality. *PLoS One.* 2014;9(2):e88283.
9. Nam KW, Kim CK, Kim TJ, et al. Predictors of 30-day mortality and the risk of recurrent systemic thromboembolism in cancer patients suffering acute ischemic stroke. *PLoS One.* 2017;12(3):e0172793.
10. Navi BB, Singer S, Merkler AE, et al. Recurrent thromboembolic events after ischemic stroke in patients with cancer. *Neurology.* 2014;83(1):26-33.
11. Kim SG, Hong JM, Kim HY, et al. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. *Stroke.* 2010;41(4):798-801.
12. Cutting S, Wettengel M, Conners JJ, Ouyang B, Busl K. Three-month outcomes are poor in stroke patients with cancer despite acute stroke treatment. *J Stroke Cerebrovasc Dis.* 2017;26(4):809-815.
13. Masrur S, Abdullah AR, Smith EE, et al. Risk of thrombolytic therapy for acute ischemic stroke in patients with current malignancy. *J Stroke Cerebrovasc Dis.* 2011;20(2):124-130.
14. Laible M, Mohlenbruch M, Hacke W, Bendszus M, Ringleb PA, Rizos T. Repeated intra-arterial thrombectomy within 72 hours in a patient with a clear contraindication for intravenous thrombolysis. *Case Rep Vasc Med.* 2015;2015:872817.
15. Merkler AE, Marcus JR, Gupta A, et al. Endovascular therapy for acute stroke in patients with cancer. *Neurohospitalist.* 2014;4(3):133-135.
16. Jung S, Jung C, Hyoung Kim J, et al. Procedural and clinical outcomes of endovascular recanalization therapy in patients with cancer-related stroke. *Interv Neuroradiol.* 2018;24(5):520-528.
17. Lee D, Lee DH, Suh DC, et al. Intra-arterial thrombectomy for acute ischaemic stroke patients with active cancer. *J Neurol.* 2019;266(9):2286-2293.
18. Cho BH, Yoon W, Kim JT, et al. Outcomes of endovascular treatment in acute ischemic stroke patients with current malignancy. *Neurol Sci.* 2020;41(2):379-385.
19. Jansen IGH, Mulder M, Goldhoorn RB, investigators MCR. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ.* 2018;360:k949.
20. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* 2015;372(1):11-20.
21. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke.* 1988;19(5):604-607.
22. Vargas M, Horcajada JP, Obach V, et al. Clinical consequences of infection in patients with acute stroke: is it prime time for further antibiotic trials? *Stroke.* 2006;37(2):461-465.
23. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol.* 2003;56(11):1129-1135.
24. Bang OY, Chung JW, Lee MJ, et al. Cancer cell-derived extracellular vesicles are associated with coagulopathy causing ischemic stroke via tissue factor-independent way: the OASIS-CANCER study. *PLoS One.* 2016;11(7):e0159170.
25. Schwarzbach CJ, Schaefer A, Ebert A, et al. Stroke and cancer: the importance of cancer-associated hypercoagulation as a possible stroke etiology. *Stroke.* 2012;43(11):3029-3034.
26. Lee MJ, Chung JW, Ahn MJ, et al. Hypercoagulability and mortality of patients with stroke and active cancer: the OASIS-CANCER study. *J Stroke.* 2017;19(1):77-87.
27. Lysov Z, Dwivedi DJ, Gould TJ, Liaw PC. Procoagulant effects of lung cancer chemotherapy: impact on microparticles and cell-free DNA. *Blood Coagul Fibrinolysis.* 2017;28(1):72-82.
28. Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. *Stroke.* 2011;42(9):2410-2418.
29. D'Souza M, Nielsen D, Svane IM, et al. The risk of cardiac events in patients receiving immune checkpoint inhibitors: a nationwide Danish study. *Eur Heart J.* 2021;42(16):1621-1631.
30. Groot AE, Treurniet KM, Jansen IGH, et al. Endovascular treatment in older adults with acute ischemic stroke in the MR CLEAN Registry. *Neurology.* 2020;95(2):e131-e9.

Clinical Outcome After Endovascular Treatment in Patients With Active Cancer and Ischemic Stroke: A MR CLEAN Registry Substudy

Merelijne A. Verschoof, Adrien E. Groot, Sebastiaan F.T.M. de Bruijn, et al.

Neurology 2022;98;e993-e1001 Published Online before print January 11, 2022
DOI 10.1212/WNL.0000000000013316