Mechanical thrombectomy beyond the circle of Willis: efficacy and safety of different techniques for M2 occlusions

Original research

Mechanical thrombectomy beyond the circle of Willis: efficacy and safety of different techniques for M2 occlusions

Leonardo Renieri ,[1] Iacopo Valente ,[2] Adam A Dmytriw ,[3] Ajit S Puri,[4] Jasmeet Singh,[4] Sergio Nappini ,[5] Patrizia Nencini,[6] Artem Kaliaev,[7] Mohamad Abdalkader ,[7] Andrea Alexandre,[2] Giuseppe Garignano,[2] Sheela Vivekanandan,[8] Reginald P Fong,[8] Carmen Parra-Fariñas ,[9] Julian Spears,[10] Santiago Gomez-Paz ,[11] Christopher Ogilvy,[11] Robert W Regenhardt ,[12] Naif Alotaibi,[13] André Beer-Furlan ,[14] Krishna C Joshi ,[14] Melanie Walker,[15] Juan Vicenty-Padilla,[16] Jean Darcourt,[17] Paul Foreman,[18] Anna L Kuhn,[4] Thanh N Nguyen ,[19] Christoph J Griessenauer,[8] Thomas R Marotta ,[9] Ajith Thomas ,[11] Aman B Patel,[13] Thabele M Leslie-Mazwi ,[13] Michael Chen ,[14] Michael R Levitt ,[15] Karen Chen ,[16,20] Christophe Cognard,[17] Alessandro Pedicelli,[2] Nicola Limbucci[1]

For numbered affiliations see end of article.

Correspondence to
Dr Iacopo Valente, UOC Radiologia e Neuroradiologia, Policlinico Universitario Agostino Gemelli, Roma, Lazio, Italy; iacopovalentemd@gmail.com

LR and IV contributed equally as first authors.

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ABSTRACT

Background M2 segment occlusions represent approximately one-third of non-lacunar ischemic stroke and can lead to permanent neurological deficits. Various techniques are available for mechanical thrombectomy beyond the circle of Willis, but data evaluating their effectiveness and safety are lacking.

Methods A retrospective review of patients with ischemic stroke undergoing mechanical thrombectomy for M2 occlusions from 13 centers in North American and Europe was performed. Tandem or multiple-territory occlusions were excluded. The primary outcome was 90-day modified Rankin Scale and reperfusion rates across stent-retriever, direct aspiration and combined techniques.

Results There were 465 patients (mean age 71.48±14.03 years, 53.1% female) with M2 occlusions who underwent mechanical thrombectomy. Stent-retriever alone was used in 133 (28.6%), direct aspiration alone in 93 (20.0%) and the combined technique in 239 (51.4%) patients. Successful reperfusion was achieved with the combined technique in 198 (82.2%; OR 2.6 (1.1–6.9)), with stent-retriever alone in 112 (84.2%; OR 9.2 (1.9–44.6)) and with direct aspiration alone in 62 (66.7%; referencecategory). Intraprocedural subarachnoid hemorrhages (iSAH) were 36 (7.7%) and were more likely to occur in patients treated with the stent-retrievers (OR 5.0 (1.1–24.3)) and combined technique (OR 4.6 (1.1–20.9)). Good clinical outcome was achieved in 260 (61.8%) patients, while 59 (14.0%) patients died. Older age, higher baseline NIHSS (National Institutes of Health Stroke Scale), parenchymal hemorrhage and iSAH were associated with poor outcome while successful recanalization and higher baseline ASPECTS (Alberta Stroke Program Early CT Score) were associated with good outcome. No differences were found among the three techniques in terms of clinical outcome.

Conclusion Stent-retrievers and a combined approach for M2 occlusions seem more effective than direct aspiration, but with higher rates of iSAH. This leads to no detectable difference in clinical outcome at 3 months.

INTRODUCTION

There has been a rapid evolution in techniques and devices for mechanical thrombectomy since the demonstration of efficacy of endovascular treatment (EVT) for large vessel occlusion (LVO) stroke in 2015.[1–7] Originally, stent-retrievers were used alone, while direct aspiration was limited by the availability of large, flexible and atraumatic catheter systems at the time of these trials. These technical barriers have subsequently been overcome, and contact aspiration is now a valid alternative to stent-retrievers for LVO. In fact, the ASTER trial has been published on this topic and showed comparable results between the two techniques,[8] while the COMPASS trial demonstrated that first-pass efficacy of primary aspiration is not inferior to stent-retrievers alone.[9] A combined approach with stent-retriever and adjunctive distal aspiration is a third commonly used endovascular option, but there is no evidence of superiority of this technique for occlusions in any specific location thus far.[10]

The efficacy of these techniques is informed by trials and retrospective series that included patients with proximal intracranial occlusions, as M2 middle cerebral artery (MCA) segment occlusions were not the principal concern in establishing a body of evidence for thrombectomy initially. Trials and large studies enrolled few M2 occlusions, despite the fact that they comprise approximately 40% of patients with ischemic stroke and a visible

occlusion on computed tomography angiography (CTA) and can lead to permanent disabilities.[11–13] This was understandable given the goal of trials at the time, but as stent-retrievers are now produced in smaller sizes and some aspiration catheters have been deployed for distal occlusions, the optimal technical approach for patients with M2 occlusion remains unclear and of increasing interest.

The objective of this study was to describe the treatment of M2 occlusions with emphasis on reperfusion efficacy and safety.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patient selection and treatment

We performed a retrospective analysis of prospectively maintained databases of 13 academic institutions in North America and Europe inclusive of all cases of EVT for acute ischemic stroke involving the M2 segment of the MCA which is classically defined as beyond the M1 bifurcation to the Sylvian segment[14 15] between January 2017 and May 2020. Due to the considerable anatomical variability, we have also taken into consideration characteristics of the occluded M2 segment such as M2 dominant versus small branch, M2 vertical versus horizontal segment, MCA bifurcation versus trifurcation, and which branch was occluded. Patients with concomitant occlusion of the ICA, M1 or with occlusion of multiple territories were excluded, as well as patients with incomplete records. Patients with a pre-stroke modified Rankin Scale (mRS) >2 were excluded from the 90-days clinical outcome analysis while they were included in the technical outcome analysis.

All eligible patients received intravenous recombinant tissue plasminogen activator (rTPA) according to standard guidelines. Patients underwent mechanical thrombectomy after non-contrast CT excluded cerebral hemorrhage or major infarct (>1/3 of the MCA territory) and multiphase computed tomography angiography (mCTA) showed an occlusion of the M2 segment. Computed topography perfusion (CTP) was added to mCTA if required by the imaging protocol of each center. Procedures were performed under general anesthesia or conscious sedation at the discretion of individual interventionalists. Mechanical thrombectomy was performed with a stent-retriever and proximal guide catheter aspiration, direct contact aspiration or a combination of stent-retriever and distal aspiration. The technique chosen was at the discretion of individual interventionalists.

Radiological and clinical follow-up were scheduled based on individual institution clinical practice. Large-bore reperfusion catheters were considered to be those having an inner lumen larger than 0.64 inches.

Clinical variables and measures of outcome

Demographics, clinical, radiological/angiographic, procedural and outcome variables were analyzed. According to the modified Treatment In Cerebral Ischemia (mTICI) scale, we reported successful and complete reperfusion rates (defined respectively as mTICI 2b-3 and mTICI 3).[16]

Parenchymal hemorrhage (PH) was defined as HI2, PH1 and PH2 according to European Cooperative Acute Stroke Study (ECASS) classification.[17]

iSAH was identified as contrast extravasation on digital subtraction angiography. Good clinical outcome was defined as mRS ≤2 at 90 days.

Statistical analysis

Continuous variables are reported as mean±SD or median (IQR), as appropriate. Categorical variables are reported as proportions. A multivariable analysis was performed using mixed effect logistic regression model with casual effect based on the hospital of treatment; we considered clinical outcome (90-days mRS) and technical outcomes (successful recanalization, complete recanalization, first-passage successful recanalization, PH, SAH) as dependent variables. Confounding factors included in the multivariable models were all the variables included in the univariate analysis with a P value <0.1 as well as age and gender. Proportions, odds ratios (ORs) and 95% confidence intervals were reported.

All variables (except for prespecified confounding factors) included in the multivariable model with a variable-inflating factor (VIF) greater than 2.5 were excluded from the analysis due to multicollinearity issues. Statistical analysis was performed with STATA 15.1 (StataCorp LLC, College Station, TX, USA).

RESULTS

A total of 4268 patients underwent mechanical thrombectomy between January 2017 and April 2020. Among them, 584 (13.8%) were treated for M2 occlusion. Eighty-nine patients were excluded due to lack of clinical outcome data while 35 were excluded for missing technical details for a total of 465 patients included in the analysis.

Patient demographics

Mean age was 71.48±14.4 years and 53.1% of the patients were female. One hundred and twenty-nine (25.6%) patients were smokers, 167 (33.7%) had atrial fibrillation, 144 (32.8%) were on antiplatelet therapy while 81 (17.4%) were on anticoagulant therapy. Two hundred and thirty-one (49.7%) patients received intravenous rtPA (alteplase). The median preprocedural National Institutes of Health Stroke Scale (NIHSS) was 14 (IQR 8–19).

Technical outcome

The most common technique reported was the combined approach totaling 239 (51.4%); stent-retrievers alone were used in 133 cases (28.6%) and direct aspiration alone in 93 cases (20.0%). A large-bore catheter was used in 51 (54.8%) direct aspiration approaches. Detailed demographic and procedural information according to approaching technique is summarized in table 1.

Overall, successful reperfusion was obtained in 372 (80.0%) cases. Successful reperfusion before switching to another technique was achieved in 112 cases with a stent-retriever (84.2%; OR 9.2 (1.9–44.6)), in 198 cases with a combined technique (82.8%; OR 2.6 (1.1–6.9)) and in 62 cases with direct aspiration alone (66.7%; reference category). Complete technical outcome results are shown in table 2.

PH was reported in 59 patients (12.7%) and iSAH in 36 (7.7%) cases. Concerning iSAH, stent-retriever and combined technique showed an increased risk of bleeding (ORs 5.0 (1.1–24.3) and 4.6 (1.1–20.9), respectively).

The adjusted analysis did nott show any significant influence of the anatomical characteristics of the M2 branch on either efficacy or safety outcomes.

Clinical outcome

Forty-four (44) patients with a pre-stroke mRS >2 were excluded from the clinical outcome analysis. Hence 421 patients were included in the clinical outcome analysis (table 3). A good

Table 1 Detailed demographic and procedural information according to technique used

Parameter	Direct aspiration	Combined	Stent-retriever	P value
n	93 (20.0%)	239 (51.4%)	133 (28.6%)	
Age (years)	72.07±12.34	71.11±14.56	71.73±15.16	0.853
Female	44 (47.3%)	130 (54.4%)	73 (54.9%)	0.453
Smoking	23 (24.7%)	69 (28.9%)	32 (24.1%)	0.426
rtPA	42 (45.2%)	120 (50.2%)	69 (51.9%)	0.593
Minutes from LKW to puncture	262 (194–385)	262 (180–453)	195.5 (150–283.5)	**0.001**
M2 dominant	84 (90.7%)	143 (59.9%)	105 (78.7%)	**<0.001**
M2 horizontal	38 (40.7%)	90 (37.7%)	54 (40.4%)	0.867
MCA trifurcation	26 (27.8%)	32 (13.5%)	38 (28.7%)	**0.003**
MCA branches				**0.014**
Superior	46 (50.0%)	108 (45.3%)	74 (55.3%)	
Middle	21 (22.2%)	21 (8.6%)	14 (10.6%)	
Inferior	26 (27.8%)	109 (45.8%)	45 (34.0%)	
Number of attempts	1.3±0.6	1.7±1.0	1.7±0.8	**<0.001**

Continuous variables are reported as mean±SD or median (IQR). Other values are n (%).
Bold type denotes statistical significance (p-value < 0.05
LKW, last known well; MCA, middle cerebral artery; rtPA, recombinant tissue plasminogen activator.

clinical outcome was achieved in 260 (61.8%) patients while 59 patients (14.0%) died. Older age (OR 0.74 (0.58–0.94), each 10 years), higher baseline NIHSS (OR 0.9 (0.86–0.94)), PH (OR 0.17 (0.06–0.49)) and SAH (OR 0.39 (0.17–0.89)) were associated with poor outcome while successful recanalization (OR 2.81 (1.39–5.65)) and higher baseline ASPECTS (OR 1.33 (1.01–1.75)) were associated with good outcome. There was no difference between the three techniques in terms of clinical outcome at multivariate adjusted analysis.

Table 2 Comparison of efficacy and safety between the three techniques

Parameter	Overall	Direct aspiration (ref.)	Combined	Stent-retriver
mTICI 2b-3	372 (80.0%)	62 (66.7%)	198 (82.8%)	112 (84.2%)
OR mTICI 2b-3	–	–	**2.6 (1.1–6.9)**	**9.2 (1.9–44.6)**
mTICI 3	205 (44.1%)	32 (34.4%)	108 (45.2%)	65 (48.9%)
OR mTICI 3	–	–	1.6 (0.6–4.0)	**3.7 (1.1–12.6)**
No. of switching	36 (7.7%)	23 (24.7%)	7 (2.9%)	6 (4.5%)
mTICI 2b-3 after switch	27 (75.0%)	17 (73.9%)	7 (100.0%)	3 (50.0%)
First-passage mTICI 2b-3	216 (46.4%)	47 (50.5%)	110 (46.0%)	59 (44.4%)
OR first-passage mTICI 2b-3	–	–	0.9 (0.3–2.0)	1.4 (0.4–4.6)
iSAH	36 (7.7%)	2 (2.1%)	22 (9.2%)	12 (9.0%)
OR iSAH	–	–	**4.6 (1.1–20.9)**	**5.0 (1.1–24.3)**
PH	59 (12.7%)	6 (6.4%)	15 (11.3%)	38 (15.9%)
OR PH	–	–	1.0 (0.3–4.0)	1.5 (0.4–5.3)

Bold type denotes statistical significance (p-value <0.05)
*Technical and safety outcomes have been adjusted for age, gender, center, minutes from LKW to puncture, M2 dominant segment, MCA trifurcation, MCA branches involved and number of attempts.
iSAH, intraprocedural subarachnoid hemorrhage; LKW, last known well; MCA, middle cerebral artery; mTICI, modified Treatment In Cerebral Ischemia; OR, odds ratio; PH, parenchymal hemorrhage; ref., reference category.

Table 3 Detailed demographic and procedural information according to clinical outcome*

Parameter	Overall	mRS 3–6	mRS 0–2	P value
n	421	161 (38.2%)	260 (61.8%)	
Age (years)	71.0±14.4	75.6±12.9	68.1±14.5	**<0.001**
Female	224 (53.2%)	95 (59.0%)	129 (49.6%)	0.061
Smoking	108 (25.6%)	36 (22.4%)	72 (27.7%)	0.223
Atrial fibrillation	142 (33.7%)	60 (37.3%)	82 (31.5%)	0.235
Anti-platelet	127 (30.2%)	54 (33.5%)	73 (28.1%)	0.242
Anti-coagulant	67 (15.9%)	30 (18.6%)	37 (14.2%)	0.234
rtPA	218 (51.8%)	76 (47.2%)	142 (54.6%)	0.140
Left-sided occlusion	253 (60.1%)	87 (54.0%)	166 (63.8%)	**0.050**
Minutes from LKW to puncture	238 (175–360)	230 (174–360)	240 (175–356)	0.573
Baseline NIHSS	14 (8–19)	18 (12–22)	10 (7–17)	**<0.001**
Baseline ASPECTS	8.86 (8.71–9.00)	8.59 (8.33–8.85)	9.02 (8.85–9.19)	**<0.001**
mCTA	232 (55.2%)	87 (54.4%)	145 (55.7%)	0.832
CTP	160 (38.1%)	21 (13%)	67 (25.7%)	0.201
Stent-retriever	119 (28.3%)	45 (27.9%)	74 (28.5%)	0.142
Direct aspiration	92 (21.8%)	43 (26.7%)	49 (18.9%)	
Combined	210 (49.9%)	73 (45.3%)	137 (52.7%)	
Procedure duration	49 (35–75)	56 (40–81)	45 (32–68)	**<0.001**
Minutes from LKW to recanalization	295 (228–431)	299 (231.5–430)	289 (226–438)	0.819
Successful recanalization	359 (85.3%)	123 (76.4%)	236 (90.8%)	**<0.001**
PH	52 (12.3%)	36 (22.4%)	16 (6.1%)	**<0.001**
SAH	79 (18.8%)	47 (29.2%)	32 (12.3%)	**<0.001**

Bold type denotes statistical significance (p-value < 0.05)
*Patients with a pre-treatment mRS >2 have been excluded.
ASPECTS, Alberta Stroke Program Early CT Score; CTP, computed tomography perfusion; iSAH, intraprocedural subarachnoid hemorrhages; LKW, last known well; mCTA, multiphase computed tomography angiography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hemorrhage; rtPA, recombinant tissue plasminogen activator.

DISCUSSION

In this series of 465 patients with acute ischemic stroke due to M2 occlusion, we report an overall rate of mTICI 2b-3 reperfusion of 85.8% (399/465) and a good clinical outcome at 3 months of 61.8% (260/421), which is similar to other retrospective series published on M2 or more distal occlusions[18 19] confirming that patients with M2 occlusions eligible for mechanical recanalization often benefit from it, as already established by recent meta-analysis and studies.[20 21] Our findings are also in line with the successful reperfusion rate of the major trials that included mainly intracranial internal carotid artery and first MCA segment occlusions which ranged from 71% to 86% mTICI 2b-3.[6–8 22] Proximal and M2 occlusions therefore appear to have a similar chance of reperfusion, likely due to the emergence of smaller size stent-retrievers as well as more flexible and thinner diameter aspiration catheters.[10]

Reperfusion rates

Concerning the efficacy of different techniques in this group of patients, our data suggest that direct aspiration alone leads to lower reperfusion rates compared with stent-retriever use alone

and stent retriever plus distal aspiration. Specifically, the use of a stent-retriever increases the chances of successful reperfusion (mTICI 2b-3) in comparison to distal aspiration alone by nearly eight times. Haussen *et al* documented a trend towards a higher rate of mTICI 2b-3 reperfusion with the 3 mm Trevo retriever compared with the 3MAX aspiration catheter for distal occlusions (84% vs 69%, p=0.05) and a higher rate of first-pass mTICI 2b-3 (62% vs 44%, p=0.03).[23] Mokin *et al* reported similar angiographic and clinical success rate for the two techniques, but in 29.5% of the cases where direct aspiration was chosen as first technique, the operator had to switch to a combined approach.[24]

Despite contact aspiration being suggested to be very effective in proximal occlusions,[8 9] the need for smaller catheters in conjunction with the differing anatomy of distal vessels has the potential to reduce its efficacy. The large-bore catheters used for proximal occlusions (0.072 inches) permit high-flow aspiration maintaining a near vacuum, while distal aspiration catheters have smaller diameters (0.035–0.041 inches) and therefore they may not necessarily provide the same performance as demonstrated in vitro.[25] Moreover, integration of clot into the catheter may occur less optimally due to the angulation of the M1-M2 junction which can result in a less favorable vector of engagement.[23 26]

In our series, a first-line strategy of aspiration in combination with stent-retrievers did not increase the efficacy of mechanical thrombectomy compared with stent-retriever use alone (82.8% vs 84.2%) which itself integrates into the clot and subsequently extracts a distal embolus efficiently. Perhaps not surprisingly then, the combined approach was superior to aspiration alone. This latter finding is not confirmed by a recent meta-analysis by Texakalidis *et al* who concluded that there was no statistical difference between the two techniques, perhaps as the study was mainly examining proximal occlusions.[27] There are no randomized trials comparing combined and stent-retriever-only techniques, aside from one study where Nogueira *et al* concluded that aspiration plus the Penumbra 3D stent-retriever was not inferior to direct aspiration alone.[28]

Interestingly in our cohort of patients, anatomical characteristics of M2 segments correlate neither with reperfusion nor safety of mechanical thrombectomy. In fact, the dominance of the branch and its orientation (vertical or horizontal) do not influence the radiological outcome, contrary to what one might expect. Few published papers have considered the anatomy of MCA as a critical feature to consider, nevertheless in M1 occlusions it seems that mechanical thrombectomy is significantly less often successful in patients with large vessel angles.[29] Our study focused on the effectiveness of different techniques, and the number of patients enrolled in the study is insufficient to be able to draw any conclusion about anatomical aspects that could influence the outcome.

Regarding the first-pass effect,[30] all three techniques were similar in achieving successful reperfusion on the first pass, and most techniques were efficient as rescue therapy in case of failure of the first-line technique. However, the number of patients studied with rescue therapy was small (7.7%).

Complications

In our cohort of patients, we encountered an overall risk of hemorrhage of 32.3%, including both PH and SAH, which was lower than that reported from the M2 occlusion subanalysis in the ASTER trial (38%).[25] This may be due to the extravasation of contrast, which appears similar on non-contrast head CT. The use of dual-energy CT post-procedure may prove helpful for this purpose in future analyses.[31 32]SAH might reasonably be considered a strictly related complication, but it does not necessarily correlate with patient neurological deterioration as would PH. Indeed, iSAH is generally caused by vessel perforation, dissections and endothelial damage due to the interventional maneuvers and/or by stretching arterioles or perforators. Specifically, we reported 7.7% of iSAH, which is similar to the data reported in the literature for proximal occlusions (5%–12%), and which may be due to the fragility of distal arteries, challenges in anatomical access, in addition to the aforementioned considerations.[19 33 34] From our data it appears that direct aspiration is less traumatic compared with mechanical thrombectomy with a stent-retriever or a combined approach, considering that the OR for iSAH was 5.0 in cases of stent-retriever use and 4.6 for the combined approach when compared with direct aspiration.

The major advantage of thromboaspiration is undoubtedly the potential to directly push the catheter to the proximal face of the clot without crossing the thrombus with a microwire and therefore minimizing the risk of blind wire advancement beyond the occlusion. Still, this maneuver is necessary in cases of mechanical thrombectomy with a stent-retriever which may also further damage the arterial endothelium during retraction causing yet additional risk of iSAH. However, this better safety profile with direct contact aspiration needs to be balanced by the potentially lower rate of reperfusion. Based on our data, the combined technique had a higher risk of iSAH as well. By contrast, we did not find a significant difference between the different techniques regarding the likely incidence of PH because they mainly follow reperfusion injury rather than being related to the technical challenges in distal clot access.

Clinical outcomes

Our study confirms that older age, higher NIHSS on onset and lower ASPECTS correlate with poor outcome for patients with M2 occlusions as previously suggested by Sarraj *et al*,[14] while we found no significant correlation between outcome and time to reperfusion.

Surprisingly, despite a significant difference in efficacy of reperfusion between the three techniques, functional independence and mortality at 90 days were not impacted. This may be related to the heterogeneity of disability in patients with medium or distal vessel occlusions, as well as right- versus left-sided M2 occlusions.

Limitations

This study has limitations inherent to all retrospective and multicenter analyses. Reperfusion grade and complications were self-adjudicated rather than with core laboratory adjudication. In addition, interventionalist discretion could have favored a specific technique with which they were more comfortable. We attempted to alleviate these factors with inclusion of consecutive cases and adjustments for centers and confounders. Another limitation is that we excluded 89 patients from this study due to lack of 90-day mRS data, which may have biased the results towards better outcomes (if patients with worse disability were being excluded for lack of follow-up) or worse outcomes (it may be easier to track mortality at 90 days, that is, if there was in-hospital death).

CONCLUSIONS

In the setting of M2 occlusions, stent-retrievers and stent-retrievers associated with distal aspiration are associated with higher rates of reperfusion compared with direct aspiration.

By contrast, direct aspiration alone appears to be the safest technique in relation to procedural complications. Clinical outcome is not affected by the technique used for endovascular reperfusion.

Author affiliations
[1]Interventional Neuroravascular Unit, University Hospital Careggi, Firenze, Italy
[2]UOC Radiologia e Neuroradiologia, Policlinico Universitario Agostino Gemelli, Roma, Italy
[3]Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[4]Division of Neuroradiology, Department of Radiology, University of Massachusetts Medical School, Worcester, Massachusetts, USA
[5]Neurovascular Interventional Unit, University Hospital Careggi, Firenze, Italy
[6]Stroke Unit, University Hospital Careggi, Firenze, Italy
[7]Department of Radiology, Boston Medical Center, Boston, Massachusetts, USA
[8]Department of Neurosurgery, Geisinger Medical Center, Danville, Pennsylvania, USA
[9]Department of Medical Imaging, Division of Diagnostic and Therapeutic Neuroradiology, St Michael's Hospital, Toronto, Ontario, Canada
[10]Division of Neurosurgery, St Michael's Hospital, Toronto, Ontario, Canada
[11]Department of Neurosurgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
[12]Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA
[13]Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts, USA
[14]Neurological Surgery, Rush University Medical Center, Chicago, Illinois, USA
[15]Department of Neurological Surgery, University of Washington School of Medicine, Seattle, Washington, USA
[16]Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts, USA
[17]Diagnostic and Therapeutic Neuroradiology, Hôpital Purpan, Toulouse, France
[18]Department of Neurosurgery, Orlando Health Corp, Orlando, Florida, USA
[19]Department of Neurology, Boston Medical Center, Boston, Massachusetts, USA
[20]Radiology, Boston Children's Hospital, Boston, Massachusetts, USA

Twitter Artem Kaliaev @artemka__crh, Santiago Gomez-Paz @SantiagoGP92, Robert W Regenhardt @rwregen, Christoph J Griessenauer @cgriessenauer, Michael Chen @dr_mchen and Michael R Levitt @DrMichaelLevitt

Collaborators Catholic University Radiology Residency Program; Pietro Trombatore, Luca Milonia.

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ORCID iDs
Leonardo Renieri http://orcid.org/0000-0001-8966-8266
Iacopo Valente http://orcid.org/0000-0002-0451-2105
Adam A Dmytriw http://orcid.org/0000-0003-0131-5699
Sergio Nappini http://orcid.org/0000-0002-2607-5815
Mohamad Abdalkader http://orcid.org/0000-0002-9528-301X
Carmen Parra-Fariñas http://orcid.org/0000-0002-6444-2188
Santiago Gomez-Paz http://orcid.org/0000-0003-2283-3612
Robert W Regenhardt http://orcid.org/0000-0003-2958-3484
André Beer-Furlan http://orcid.org/0000-0001-9732-1748
Krishna C Joshi http://orcid.org/0000-0002-3564-6958
Thanh N Nguyen http://orcid.org/0000-0002-2810-1685
Thomas R Marotta http://orcid.org/0000-0002-2480-2054
Ajith Thomas http://orcid.org/0000-0003-4412-3152
Thabele M Leslie-Mazwi http://orcid.org/0000-0002-4191-2466
Michael Chen http://orcid.org/0000-0003-2412-8167
Michael R Levitt http://orcid.org/0000-0003-3612-3347
Karen Chen http://orcid.org/0000-0002-5034-3867

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