Imaging of CNS lymphoma
Newly recognized CNS tumors from WHO 2021 classification
Stent-assisted coiling in the treatment of unruptured intracranial aneurysms
Incidental MRI findings in research volunteers

Official Journal ASNR • ASFNR • ASHNR • ASPNR • ASSR
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VIA 21, 27, 33 - The VIA Microcatheter is intended for the introduction of interventional devices (such as the WEB device/stents/flow diverters) and infusion of diagnostic agents (such as contrast media) into the neuro, peripheral, and coronary vasculature.

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The VIA Microcatheter is contraindicated for use with liquid embolic materials, such as n-butyl 2-cyanoacrylate or ethylene vinyl alcohol & DMSO (dimethyl sulfoxide).

The device should only be used by physicians who have undergone training in all aspects of the WEB Aneurysm Embolization System procedure as prescribed by the manufacturer.

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VUEWAY™ (gadopiclenol) solution for injection

Indications
VUEWAY injection is indicated in adults and children aged 2 years and older for use with magnetic resonance imaging (MRI) to detect and visualize lesions with abnormal vascularity in:

- the central nervous system (brain, spine and surrounding tissues),
- the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system).

IMPORTANT SAFETY INFORMATION

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR < 30 mL/min/1.73 m²), or
  - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.

- For patients at highest risk for NSF, do not exceed the recommended VUEWAY dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

Contraindications
VUEWAY injection is contraindicated in patients with history of hypersensitivity reactions to VUEWAY.

Warnings
Risk of nephrogenic systemic fibrosis is increased in patients using GBCA agents that have impaired elimination of the drugs, with the highest risk in patients chronic, severe kidney disease as well as patients with acute kidney injury. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities.

Hypersensitivity reactions, including serious hypersensitivity reactions, could occur during use or shortly following VUEWAY administration. Assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders, administer VUEWAY only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, and observe patients for signs and symptoms of hypersensitivity reactions after administration.
**Gadolinium retention** can be for months or years in several organs after administration. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (brain, skin, kidney, liver and spleen). Minimize repetitive GBCA imaging studies, particularly closely spaced studies, when possible.

**Acute kidney injury** requiring dialysis has occurred with the use of GBCAs in patients with chronically reduced renal function. The risk of acute kidney injury may increase with increasing dose of the contrast agent.

Ensure catheter and venous patency before injecting as *extravasation* may occur, and cause tissue irritation.

VUEWAY may impair the visualization of lesions seen on non-contrast MRI. Therefore, caution should be exercised when Vueway MRI scans are interpreted without a companion non-contrast MRI scan.

The most common adverse reactions (incidence ≥ 0.5%) are injection site pain (0.7%), and headache (0.7%).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

Please see BRIEF SUMMARY of Prescribing Information for VUEWAY, including BOXED WARNING on Nephrogenic Systemic Fibrosis.
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INSTRUCTIONS AND USAGE 
Vueway™ (gadopentetate) injection, for intravenous use 

BRIEF SUMMARY: Please see package insert for full prescribing information.

PATIENTS COUNSELING INFORMATION 

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In Planning for Brain Metastases Treatment, Imaging may be the Missing Link in Cost Containment

When faced with a patient presenting with metastatic brain cancer, determining whether to use up-front stereotactic radiosurgery (SRS) vs. first treating with whole brain radiotherapy (WBRT) is a significant clinical decision.

WBRT: The whole story on cognitive impairment
While whole brain radiotherapy (WBRT) has been the main treatment option for many years, experts agree that it often results in cognitive deterioration and a negative impact on quality of life. This mental decline has a devastating impact on patients and their families and adds ongoing costs for the healthcare systems managing these symptoms.

Using WBRT instead of SRS in some patients is estimated to decrease the total costs of brain metastasis management, though with increased toxicity.

SRS: Fewer side effects but greater risk of missed tumors
The cost of upfront SRS is the greatest contributor to cost of brain metastasis management. SRS is often more expensive than WBRT. What’s more, multiple applications of SRS can increase the cost of treatment greatly.

Stereotactic radiosurgery (SRS) has far fewer side effects, but upfront use of SRS is expensive and can carry the risk of missed tumors, requiring repeat procedures such as salvage SRS.

Number of lesions and lesion size are key factors to be considered when determining the treatment plan for these patients. It follows that increased diagnostic information and accuracy could be beneficial in directing the proper therapy and improving overall long-term patient outcomes and containing costs. Getting the diagnosis right the first time is crucial to ensure proper treatment begins quickly, and high cost/high stakes procedures such as SRS need precise surgical planning.

What does optimal visualization mean for outcomes and cost?
For surgical planning with SRS, radiologists need the best visualization achievable to accurately count the number and size of the lesions. These metrics are the key predictors of the need for SRS, WBRT, or a combination of both.

By selecting the ideal contrast agent and equipment protocols, neuroradiologists can identify the proximate numbers of metastases for upfront treatment and reduced salvage treatment occurrences.

The role of radiology
As medical care for oncology patients continues to evolve, it will be increasingly important to assess the cost of various interventions given the often-limited life expectancy of cancer patients, the rising costs of cancer therapy, and the increasing prevalence of cancer in an aging population.

Through seeing all the tumors and tumor borders as clearly as technology allows, radiology can play a part in ensuring that proper treatment can begin quickly, while containing costs through optimized patient care. Efforts to carefully manage treatment approaches require improvements in protocol design, contrast administration in imaging, and utilizing multimodal imaging approaches.

In this era of precision medicine, radiology departments’ contribution to this improved standard of care will have significant short and long-term implications by reducing cost of care, providing a more proximate diagnosis, and ensuring optimal patient outcomes.


For more information on MRI contrast agents, precision medicine, and reducing cost of care please visit braccomr.com

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The Helix nebula (NGC 7293) is a poorly named “planetary nebula” located in the constellation of Aquarius, and sometimes referred to as the “Eye of Sauron.” Planetary nebulas have nothing to do with planets and were erroneously named because they seemed to resemble gas-giant planets with the equipment of the time (circa 1824). The dying of a star causes the ejection of its outer gaseous layers and leaves behind a white dwarf star (center of the eye). This image was acquired as a series of 96 5-minute exposures (8 hours) using red, green, and blue filters. The telescope was a 12.5” Ritchey-Chretien telescope, f/9 on a Paramount ME mount situated in Australia. The camera was an Apogee Alta U16 CCD with Astrodon filters. The images were processed using PixInsight, Photoshop, and Topaz Labs Adjust AI and DeNoise AI.

Jeffrey S. Ross, Mayo Clinic, Phoenix, Arizona
Imaging of Lymphomas Involving the CNS: An Update-Review of the Full Spectrum of Disease with an Emphasis on the World Health Organization Classifications of CNS Tumors 2021 and Hematolymphoid Tumors 2022

A. Pons-Escoda, P. Naval-Baudin, R. Velasco, N. Vidal, and C. Majós

ABSTRACT

SUMMARY: Lymphomas of the CNS are the second most frequent primary brain malignancy in adults after gliomas, accounting for 7% of all malignant tumors. A presurgical suspicion of lymphoma greatly impacts patient management. The radiologic features of this tumor have been widely covered in the literature for decades, but under current classifications, mainly corresponding to the most common presentations of the most frequent type: primary diffuse large B-cell lymphoma of the CNS. Nevertheless, rarer presentations of this specific lymphoma and of other World Health Organization lymphoma subtypes with different imaging features are rarely treated. Moreover, important advances in imaging techniques, changing epidemiologic factors with relevant impact on these tumors (eg, immunodeficiency/dysregulation), and recent updates of the World Health Organization Classification of CNS Tumors 2021 and Hematolymphoid Tumors 2022 may have rendered some accepted concepts outdated. In this article, the authors aim to fulfill a critical need by providing a complete update-review, emphasizing the latest clinical-radiologic features of the full spectrum of lymphomas involving the CNS.

ABBREVIATIONS: ALK+/ALK− = anaplastic lymphoma kinase positive and negative; CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; MALT = mucosa-associated lymphoid tissue; NK = natural killer; PSR = percentage of signal recovery; WHO = World Health Organization

Lymphomas of the CNS are the second most frequent primary brain malignancy in adults after gliomas, accounting for 7% of all malignant tumors. A presurgical suspicion of lymphoma greatly impacts patient management. The radiologic features of this tumor have been widely covered in the literature for decades, but under current classifications, mainly corresponding to the most common presentations of the most frequent type: primary diffuse large B-cell lymphoma of the CNS. Nevertheless, rarer presentations of this specific lymphoma and of other World Health Organization lymphoma subtypes with different imaging features are rarely treated. Moreover, important advances in imaging techniques, changing epidemiologic factors with relevant impact on these tumors (eg, immunodeficiency/dysregulation), and recent updates of the World Health Organization Classification of CNS Tumors 2021 and Hematolymphoid Tumors 2022 may have rendered some accepted concepts outdated.

In this article, the authors aim to fulfill a critical need by providing a complete update-review, emphasizing the latest clinical-radiologic features of the full spectrum of lymphomas involving the CNS.

WHO Classification of Tumors, 5th Edition Insights. Some basic concepts regarding WHO classifications need to be understood for an optimally up-to-date comprehension of lymphomas in the CNS. First, these tumors fall between two 5th edition WHO classifications: the CNS2 and the hematolymphoid. Second, despite impressive advances in molecular pathology, the mainstay in lymphomas remains histology of biopsy specimens; this differs greatly from other brain tumors such as gliomas, for which molecular pathology is vital. Nevertheless, clinically relevant pathogenesis, mutation profiles, and genetic drivers have been characterized in recent years. Recurrent mutations frequently
activate the B-cell receptor, toll-like receptor, and NF-κB pathways, and alterations in genes involved in chromatin structure and modification, cell-cycle regulation, and immune recognition are common. MYD88 and CD79B mutations may be of clinical interest because they can be detected in several body fluids (plasma and CSF), potentially assisting in disease-monitoring under treatment and in minimally-invasive initial diagnosis. Also, knowledge of genetically activated pathways, tumor immune microenvironment, and expression of immune-response biomarkers may point to specific treatment targets. Finally, lymphoma classifications include clinical factors, especially regarding the immune status of patients, which plays an essential role in tumor classification with important treatment implications.2,4

Updates. Thus, some changes may be identified in the updated WHO Classifications of CNS Tumors 2021 and Hematolymphoid Tumors 2022, first in CNS immunodeficiency-associated lymphoma. Whereas the prior CNS classification included a heterogeneous group of diseases primarily defined by the patient immunodeficiency setting, currently, it is exclusively defined as DLBCL and EBV positive (both essential criteria) lymphoma.2 Moreover, the current spectrum of immunodeficiency includes immune-dysregulation according to the hematolymphoid classification, in which immunocompromised settings without a fully demonstrable immunodeficiency, such as immunosenescence (among others), are included.2,4

Next, a change in terminology is recommended in the upcoming hematolymphoid classification, representing a paradigm shift. Currently, the type of immunodeficiency-associated lymphoma is not first determined by the immunodeficiency/dysregulation setting, as in the previous classification (eg, AIDS-related DLBCL). Instead, it is defined primarily by the tumor histology with the so-called 3-part nomenclature, composed of the following: 1) histologic lesion, 2) oncogenic virus status, and 3) immunodeficiency background of the patient (eg, DLBCL, EBV-positive, and autoimmune setting).4 This integrated nomenclature allows the grouping of specific types of immunodeficiency-associated lymphomas (such as DLBCL EBV-positive), despite the underlying immunodeficiency/dysregulation, to better define the unique shared pathogenetic mechanisms.3,9,10

On the other hand, lymphomatoid granulomatosis is no longer considered an immunodeficiency-associated entity. It occurs exclusively in immunocompetent patients, and in the case of an underlying immunodeficiency, it should be considered a subtype of a polymorphic lymphoproliferative disorder.4

Also, according to the WHO classification of hematolymphoid tumors, the term primary CNS lymphoma may be considered imprecise, and it is no longer recommended by the WHO classification of hematolymphoid tumors2 for referring specifically to primary DLBCL of the CNS, which is the currently preferred term.2,4

It usually appears as single or multiple (30%–35%) parenchymal lesions, located supratentorially (>80%), with a particular affinity for the basal ganglia, periventricular regions, midline, and corpus callosum (>45%). It is also frequent in brain hemispheres (≈40%), rarely found in the posterior fossa, and exceptionally in the spinal cord (Fig 1).2 Associated leptomeningeal or subependymal enhancement is characteristic, but an exclusive presentation of the disease in this location may raise suspicion of secondary lymphoma. The typical perivascular histologic pattern also carries a characteristic perivascular enhancement on imaging (Fig 1). Parenchymal lesions are most frequently solid and homogeneous, but their presentation can range from well-defined expansive to ill-defined infiltrative lesions.2,5,7,11

Notably, these lesions are frequently hyperattenuating on NCCT,2,3,7,11 which is important to keep in mind because CT is the first-line radiologic examination and suspicion at this point may lead to corticoid avoidance (Fig 1). If administered, corticoids can complicate subsequent imaging and histologic diagnosis.2,3,12

Regarding specific tumor MR imaging features, lymphoma typically appears hypointense on T2WI with marked diffusion restriction on DWI. Nevertheless, a T2-blackout effect consisting of a persistent hypointensity on b = 1000 images due to very low T2 signal may lead to misinterpretation. Thus, ADC map hypointensity might be more reliable than b = 1000 hyperintensity in assessing actual diffusion restriction.2,5,7,11 NCCT hyperattenuation, low T2 signal, and diffusion restriction correlate with high cellularity on histology, with Ki-67 proliferation indexes usually above 90% (Fig 1).13

Historically, the presence of hemorrhage or signs of necrosis on preoperative imaging in immunocompetent patients have been considered a factor arguing strongly against a diagnosis of lymphoma.14 However, the histologic appearance of tumor barriers (eg, the blood-brain barrier). However, large B-cell lymphomas occurring in the dura (dural lymphoma) or inside the brain vessels (intravascular lymphoma) escape these immune privileges and are, therefore, classified separately.2,4

With all these upgraded concepts in mind, the authors aim to provide a complete update-review of imaging features of the full spectrum of lymphomas involving the CNS, mainly based on those entities included in the 5th edition WHO Classification of Tumors of the CNS 2021.2 Primary DLBCL of the CNS, immunodeficiency-associated CNS lymphoma, lymphomatoid granulomatosis, intravascular large B-cell lymphoma of the CNS, mucosa-associated lymphoid tissue (MALT) lymphoma of the dura, other low-grade B-cell lymphomas of the CNS, anaplastic large-cell lymphoma (anaplastic lymphoma kinase positive and negative [ALK+/ALK–]), and T-cell and natural killer (NK)/T-cell lymphoma are discussed. Finally, the clinical-radiologic entity “lymphomatosis cerebri” and secondary lymphomas are also reviewed.

Imaging of CNS Lymphomas
Primary DLBCL of the CNS. Primary DLBCL of the CNS corresponds to 80%–85% of all CNS lymphomas, occurs almost always in immunocompetent patients, is EBV-negative, and is of unknown etiology.2 The term primary CNS lymphoma may be considered imprecise, and it is no longer recommended by the WHO classification of hematolymphoid tumors2 for referring specifically to primary DLBCL of the CNS, which is the currently preferred term.2,4

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samples frequently includes hemorrhagic tumors with central necrosis. Accordingly, recent literature reports the presence of hemorrhage on imaging in up to 50% of patients evaluated with SWI (20% with T2WI) and heterogeneous or ring enhancement (usually associated with necrosis) in up to 10%–15% of cases. Therefore, the authors discourage this classic assumption and believe that a certain degree of hemorrhage and heterogeneous or ring enhancements does not rule out suspicion of lymphoma, considering other imaging features as well (Fig 2).

Regarding quantitative imaging techniques beyond DWI, 1H-MR spectroscopy and DSC-PWI, included in consensus recommendations for imaging CNS lymphoma, have shown promising results for presurgical diagnosis. Attention must be paid to pulse-sequence parameters (TE, TR, flip angle), prebolus usage, and leakage corrections for DSC-PWI, but in general terms, this tumor shows low-to-intermediate CBV, a high percentage of signal recovery (PSR), and characteristic time-intensity curve morphology. Lower CBV values in lymphomas have paradoxically been related to a worse prognosis of survival. 1H-MR spectroscopy can also reinforce a presurgical suspicion in basically 2 ways: Short TE depicts much lower mIns (described as a glial marker) than that associated with enhancing non-necrotic astrocytoma (ie, grade 3), and long TE shows much lower mobile lipids (associated with necrosis) than glioblastoma or metastasis (Fig 2).

Brain FDG-PET may play a role in the presurgical differentiation of lymphoma and other malignant brain tumors such as glioblastoma and metastasis because most lymphoma lesions are highly FDG-avid, with homogeneous uptake.

As an additional comment on primary DLBCL of the CNS, it has been reported that “sentinel” inflammatory lesions, which may disappear after anti-inflammatory treatment, can precede the diagnosis of lymphoma by up to 2 years, so attention must be paid to the patient’s history of prior inflammatory brain lesions (Fig 3).

Immunodeficiency-Associated CNS Lymphoma. According to the latest WHO classification, the immunodeficiency-associated CNS lymphoma subtype specifically corresponds to primary DLBCL of the CNS, EBV-positive. Indeed, large B-cell histology and lymphotropic EBV tissue–positivity are currently the essential diagnostic criteria for immunodeficiency-associated lymphoma of the CNS. It represents 8%–10% of all primary CNS lymphomas. Despite being considered an infrequent entity, this is the second most frequent type of primary lymphoma of the CNS. Its clinical context has changed during recent decades. Whereas in the 1990s, AIDS due to HIV was the leading cause, currently and especially in more developed countries, other causes predominate, such as post transplant status, autoimmune disease, and iatrogenesis. This shift in the mechanisms of immunodeficiency and other developments in patient monitoring as well as in imaging techniques have also resulted in a change in the main differential diagnoses to consider. Currently, therefore, glioblastoma or metastases are more likely than opportunistic infections, in contrast to previous decades.

Morphologic imaging of this lymphoma is quite characteristic, and the opposite of that of the “typical” CNS lymphoma. It can
be deep or hemispheric, with a slightly greater tendency to multiplicity. It is almost constantly highly necrotic with ring enhancement and intermediate-to-prominent signs of hemorrhage. T2WI and DWI signal patterns are both variable and inconsistent. In summary, it is a tumor that differs from the typical appearance of lymphoma and, rather, presents more like the main differential diagnoses, which are glioblastoma and metastasis.8,29,30 A characteristic T2WI heterogeneous hypointensity of the nonenhancing “necrosis,” not corresponding to blood products or mineralization, has recently been suggested in these tumors, in contrast to the usual hyperintense T2 signal of nonhemorrhagic necrosis in other tumors (Fig 4).8

While conventional imaging is often insufficient to reach a presurgical diagnosis of this challenging entity, quantitative imaging, especially DSC-PWI, can provide diagnostic clues. Indeed, the perfusion features of this lymphoma follow those of low-to-intermediate CBV, high PSR, and the characteristic time-intensity curve morphology when depicting an ROI in the solid parts of tumors (Fig 4).8 Finally, the 1H-MR spectroscopy pattern seems of low value for presurgical characterization as lymphoma because this tumor has prominent mobile lipids overlapping with necrotic glioblastomas or metastasis.20

In conclusion, we suggest that in dealing with a necrohemorrhagic tumor, potential immunodeficiency/dysregulation of the patient must be thoroughly examined. If this cannot be ruled out, DLBCL EBV-positive should be considered, and careful DSC-PWI assessment can provide a presurgical diagnostic clue.

Lymphomatoid Granulomatosis. According to the new WHO classification of hematolymphoid tumors, lymphomatoid granulomatosis is a lymphoproliferative disorder with large atypical EBV-positive B-cells, T-cell infiltration, and tissue necrosis occurring exclusively in immunocompetent patients.4 Previously, it was included in the group of immunodeficiency-associated entities, but currently, the identification of an underlying immunocompromised status rules out lymphomatoid granulomatosis, and it should instead be considered a subtype of a polymorphic lymphoproliferative disorder in the setting of immunodeficiency/dysregulation.4 Lymphomatoid granulomatosis is a very rare entity that exceptionally occurs primarily in the CNS, though CNS involvement is usually secondary. It represents a spectrum of lymphoid disease graded from 1 to 3, with corresponding degrees of aggressiveness from indolent to very aggressive.2,4

On imaging, typical findings are those of secondary lymphoma with frequent subependymal or leptomeningeal involvement and perivascular enhancement. Occasionally, it may be angiocentric and angiodestructive, resembling intravascular lymphoma. When there is isolated CNS involvement, it usually corresponds to grade 3 disease, and brain biopsy demonstrates DLBCL EBV-positive,24 in which case imaging findings may consist of masslike lesions with hemorrhage and necrosis.4,31,32

In the recent literature, lymphomatoid granulomatosis has been correlated with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Some authors hypothesize that this entity is a kind of a sentinel
lesion, while others postulate that CLIPPERS may be an inflammatory response to lymphomatous tumor cells, responding to corticosteroids preceding the definitive tumor recurrence.33,34

Intravascular Large B-Cell Lymphoma of the CNS. Intravascular large B-cell lymphoma of the CNS is defined by the selective proliferation of malignant B large-tumor cells within the brain vessels, particularly small- to medium-sized blood vessels, without or with minimal parenchymal extension. The tumor cells may occlude vessels causing patched bleeding and ischemia. Also, it is not exceptional for some tumor cells to extravasate beyond the vessels, focally reaching brain parenchyma. Regarding clinical presentation, stroke-like symptoms are typical, though not always present.35

The main phenomena detected on imaging are ischemic and hemorrhagic lesions, which usually suggest the differential with vasculitis, emboli, or hypercoagulability. The ischemia-like lesions appear dynamic and evanescent between near-in-time imaging follow-ups. Furthermore, those possible tumor cells that extravasate beyond the vessels may focally reach the brain parenchyma, forming tumor islands that can appear as enlarging areas of parenchymal enhancement.2,36 Morphologic imaging features on these enhancing islands may be helpful for presurgical suspicion because they can express the signal characteristics of typical lymphoma. In addition, ependymal and leptomeningeal enhancement may also be present.36,37 Advanced imaging features may include a tumoral pattern on $^1$H-MR spectroscopy with high Cho to NAA ratios, as well as a characteristic DSC-PWI pattern with shortened MTT (differing from ischemic lesions), low-to-intermediate CBV, high PSR, and the characteristic time-intensity curve morphology of lymphomas in the CNS.7,18,20

In summary, this entity should be kept in mind whenever encountering MR imaging with hemorrhage and multiple dynamic ischemic lesions on T2WI and DWI, enlarging parenchymal enhancement, and possible associated leptomeningeal or subependymal disease (Fig 5).36,37

**FIG 4.** Primary DLBCLs of the CNS, EBV-positive (immunodeficiency/dysregulation-associated). Single (A) and multiple (B) lesions with prominent necrosis (C and E) and tumoral hemorrhage (D and F). Heterogeneous deep T2 hypointensity (H) of the nonenhancing central content (G) of lesions, so-called necrosis. Low-intermediate CBV on the corrected color map (I) and DSC-PWI time-intensity curve with high PSR (J), also very characteristic of this lymphoma subtype.
MALT Lymphoma of the Dura. Lymphomas arising primarily in the dura are rare (≈1%) and usually correspond to MALT lymphoma. Occasionally, large B-cell lymphoma may also be primarily dural. Etiology and underlying associations are unknown.2,38

On conventional imaging, they appear as extra-axial lesions with a wide dural base, soft attachment angles, and a possible CSF cleft between the lesion and brain parenchyma. In addition, edema or brain tissue infiltration can occur. They usually appear

FIG 5. Intravascular lymphoma (A–D). Acute patched ischemia-like lesions on DWI (A), hemorrhages (B), and an area of enhancement (C), which grows on the subsequent few days of imaging control (D). Dashed arrow in C–D indicates the growth of the same enhancing lesion in few days. DLBCL following a lymphomatosis cerebri pattern (E–J): extensive, patched, bilateral, and diffuse FLAIR hyperintensity on the basal ganglia (E) and white matter (F), with an area of enhancement in the left cerebellum (H) and associated leptomeningeal disease (arrow in H). Intermediate CBV in DSC-PWI color maps (I) and characteristic high PSR and time-intensity curve morphology (J). Tumoral pattern on 1H-MR spectroscopy at long TE with a high Cho-to-NAA ratio (H) and absent mIns at the short TE (not shown), helpful in the differential diagnosis with nontumoral entities and gliomatosis cerebri, respectively.
FIG 6. Dural lymphomas. MALT dural lymphoma (A–D) with extra-axial lesion features such as a CSF cleft (A) and a wide-implantation dural base with soft marginal angles (C), as well as T2-hypointensity (A) and diffusion restriction (B). Almost normal calvarial bone; only subtle sclerosis seen (D), despite the great soft-tissue component on both sides of the diploe (A–C). Similar imaging features with minimal bone destruction and a subtle permeative pattern (F) in comparison with the prominent soft-tissue component (E) in another diffuse large B-cell dural lymphoma (E and F).

FIG 7. NK/T-cell lymphoma presenting with a lymphomatosis cerebri radiologic pattern (A–C). Patched and diffuse, bilateral and asymmetric, deep and subcortical, hyperintense lesions on FLAIR (A and B) without contrast enhancement (C).

homogeneous, NCCT hyperattenuated, T2WI hypointense, and with restricted diffusion; however, these features overlap with those of the most frequent extra-axial tumor in adults, meningioma (Fig 6).39,40

Regarding advanced imaging, $^1$H-MR spectroscopy can be of help for the differential diagnosis because meningiomas characteristically present with alanine, metastases present abundant mobile lipids, and the rarer solitary fibrous tumors (formerly termed hemangiopericytoma) show a high myo-inositol peak.39

A clue for the presurgical suspicion of this tumor is provided by a characteristic pattern of bone infiltration or transdiploic extension. Characteristically, lymphoma presents as an extensive soft-tissue mass without bone destruction (normal bone to subtle permeative patterns) (Fig 6). This pattern is explained by the extension of tumor cells through Haversian canals. It differs from what is seen in meningiomas with hyperostosis or in plasmacytoma or metastasis with aggressive lytic destruction.39

Other Low-Grade B-Cell Lymphomas of the CNS, Anaplastic Large Cell Lymphoma ALK+/ALK–, T-Cell and Natural Killer (NK)/T-Cell Lymphoma. The CNS WHO classification 2021 includes low-grade B-cell lymphoma of the CNS, ALK+/ALK–, T-Cell, and NK/T-cell lymphomas classified as miscellaneous, rare lymphomas in the CNS.2 They represent a heterogeneous group of tumors with scarce evidence of concrete imaging findings. While low-grade B-cell lymphomas may occasionally appear as lymphoma-like lesions, other very different radiologic appearances are described, such as resembling edema, glial tumor, meningioma, and gliosis.41 Regarding anaplastic large-cell and T-cell or NK/T-cell lymphomas, some authors postulate that they may resemble lymphoma or lymphomatosis cerebri on imaging, with other nonspecific presentations also possible (Fig 7). In summary, very heterogeneous imaging presentations, occasionally resembling lymphoma, can be seen in this heterogeneous group of exceptional entities.41–43

Lymphomatosis Cerebri. Lymphomatosis cerebri corresponds to a clinical-radiologic pattern that is not included as a concrete histopathologic WHO entity. It may be observed in the context of different histologic lymphoma subtypes, but in most cases, it corresponds to primary DLBCL of the CNS. The typical clinical presentation is a subacute onset of dementia, cognitive impairment, and personality changes.44,45

It consists of a nonenhancing or scarcely-enhancing (30%) T2-FLAIR hyperintense infiltration of brain tissue. It is usually located in white matter regions, with different distributions ranging from focal to patched or diffuse. The main differential includes gliomatosis cerebri (also considered a radiologic pattern and not a WHO entity) and inflammatory and toxic-metabolic diseases. Of note, in this form of CNS lymphoma, brain lesions may be highly variable and change between near-in-time follow-up scans.44–47

In line with what was detailed in the intravascular lymphoma section, the detection of a tumoral pattern on $^1$H-MR spectroscopy without relevant amount of mlNs (potential glial marker present in gliomatosis) in abnormal areas of T2-FLAIR hyperintensity, as well as the above-described characteristic DSC-PWI pattern in the possible enhancing lesions, supports presurgical suspicion46,47 (Fig 5).

Secondary Lymphomas of the CNS. Secondary lymphoma refers to the CNS spread of lymphoma that originated elsewhere. It may be as an isolated recurrence or as a synchronic systemic disease with an overall incidence of around 5%–10% in patients with systemic lymphomas, usually non-Hodgkins. Its occurrence is directly correlated with pathologic aggressiveness and ranges from <3% in the indolent, less-aggressive histologies to as high as 50% in the very aggressive ones such as Burkitt lymphoma.48
Primary DLBCLs of the CNS present as homogeneous lesions, hyperdense on NECT, T2 hypointense, and with restricted diffusion. The presence of a certain degree of hemorrhage or signs of necrosis should not rule out their presurgical diagnosis.

2) Immunodeficiency-associated lymphomas (primary DLBCLs of the CNS, EBV-positive) appear as necrohemorrhagic tumors in potentially immunocompromised hosts. Special attention must be paid to the features of DSC-PWI, which may provide findings that suggest lymphoma.

3) Dural lymphoma should be suspected when a disproportionate soft-tissue mass without relevant bone destruction is identified in an extra-axial transdiploic tumor.

4) Intravascular lymphoma and lymphomatosis cerebri may be evolutive diagnoses of suspicion when dynamically changing T2-FLAIR areas of signal abnormality (and hemorrhage in intravascular lymphoma) are found. Also, attention must be paid to leptomeningeal and subependymal enhancement.

5) DSC-PWI and 1H-MRS provide clues of great help in the differential diagnosis for each lymphoma subtype.

6) Secondary lymphomas often appear as parenchymal lesions. Isolated leptomeningeal or subependymal disease is characteristic but apparently less prevalent than formerly assumed.

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**CONCLUSIONS**

The classification of CNS lymphomas is evolving. The radiologist plays a key role in the initial management of lymphomas, and a failure to suggest the possibility of this diagnosis on initial imaging may have a negative clinical impact. For this reason, the radiologist needs to be aware of the full spectrum of imaging presentations of CNS lymphoma. In this sense, we note some key points:


Newly Recognized CNS Tumors in the 2021 World Health Organization Classification: Imaging Overview with Histopathologic and Genetic Correlation


ABSTRACT

SUMMARY: In 2021, the World Health Organization released an updated classification of CNS tumors. This update reflects the growing understanding of the importance of genetic alterations related to tumor pathogenesis, prognosis, and potential targeted treatments and introduces 22 newly recognized tumor types. Herein, we review these 22 newly recognized entities and emphasize their imaging appearance with correlation to histologic and genetic features.

ABBRÉVIATIONS: AT/RT = atypical teratoid/rhabdoid tumor; cIMPACT-NOW = Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy-Not Official WHO; GFAP = glial fibrillary acidic protein; MAPK = mitogen-activated protein kinase; NEC = not elsewhere classified; NOS = not otherwise specified; PFA and PFB = posterior fossa ependymoma groups A and B; WHO = World Health Organization; WHO CNS5 = World Health Organization Classification of Tumors of the Central Nervous System, fifth edition; IDH = isocitrate dehydrogenase.


The continued discovery of pathologically relevant molecular markers, along with an improved understanding of secondary alterations in tumor biology and clinical course, has led to recognition of 22 new tumor types, in addition to nomenclature changes to the existing classification. Three provisional entities are included, which appear clinicopathologically distinct but await additional studies before full acceptance.

Despite the increasing realization of the altered molecular profile and clinical course, the imaging data on the newly recognized entities remain scarce, mostly confined to case reports and small case series. Herein, we present a consolidated review of the WHO CNS5 new tumor types with emphasis on the common imaging findings. A brief review of the general changes to the tumor taxonomy, nomenclature, and grading system is also presented.

Immunohistochemistry and Molecular Markers

Basic histology has been the backbone of previous WHO classifications of >100 known CNS tumors. Under these classifications, however, there was marked interobserver variability and poor differentiation of tumors with diverse biologic behavior. Immunohistochemistry provided major insights into the cellular markers of tumor phenotype and stronger correlations with tumor behavior, resulting in improved standardization. This information has been in routine use for more than a decade with continual improvements and discovery of new immunohistochemical stains. In 2016, for the first time, molecular markers were used in addition to histology for the classification of CNS tumors. WHO CNS5 makes a substantial addition of specific genetic markers to immunohistochemistry and histology. Epigenetic markers, particularly alterations in DNA methylation, have also been added. These have proved immensely valuable not only for diagnosis but also for prognosis and treatment guidance.

During the past decade, DNA methylation profiling has emerged as a powerful tool for research, which has started making its way into the classification system. At present, it can assess the methylation status of 850,000 cytosine-guanine sites across the human genome with huge data sets matched through standardized controls, providing great precision in tumor identification. Using these techniques, the German Cancer Research Center and Heidelberg University have provided a reference cohort for almost
all known tumor entities (www.molecularneuropathology.org). Machine learning tools can easily and accurately match a sample cohort with the references in the data base. At present, 4 of the newly recognized tumors use unique methylation profiles as part of their defining characteristics (high-grade astrocytoma with piloid features, diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters, and posterior fossa ependymoma, groups A and B [PFA and PFB]).

**Tumor Taxonomy and Nomenclature**

WHO CNS5 recognizes the variability in the need for molecular marker–based diagnoses. Some tumors have molecular characteristics that enable a complete diagnosis, whereas other tumors do not require a molecular approach for diagnosis. Thus, the current hybrid taxonomy is thought to represent an intermediate stage preceding even more precise future classifications. The only pertinent changes to the current taxonomy are “type” replacing “entity” and “subtype” replacing “variant.”

WHO CNS5 attempts to make nomenclature more consistent and simpler per the 2019 cIMPACT-NOW Utrecht meeting recommendations. WHO CNS5 uses simplified tumor names and only includes location, age, or genetic modifiers with established clinical utility. Nevertheless, the nomenclature changes are not uniformly applied because several historical terms are deeply ingrained in the literature (eg, medulloblastoma, myxopapillary ependymoma, pleomorphic xanthoastrocytoma), and name changes could be substantially disruptive to clinical care and scientific experiments. Gene and protein nomenclature has been updated to bring consistency across other existing guidelines.

**CNS Tumor Grading**

Two noteworthy changes to the grading system include the use of Arabic instead of Roman numerals and the use of tumor grades within types. For example, anaplastic astrocytoma, which was WHO grade III, is no longer a tumor type. Rather, an isocitrate dehydrogenase (IDH)-mutant tumor is now categorized as grade 2, 3, or 4 based on a combination of histologic and molecular information. Both changes ensure more nomenclature uniformity across classification systems of non-CNS tumors. Additionally, the use of tumor grades within types allows more flexibility, while at the same time emphasizing biologic similarity within tumor types.

**Not Otherwise Specified and Not Elsewhere Classified**

Not otherwise specified (NOS) implies a lack of or failure to obtain available molecular, histologic, or genetic information, which limits making a specific diagnosis. Not elsewhere classified (NEC) refers to cases in which the diagnostic testing has been successful but the results do not readily conform to a standard diagnosis under WHO CNS5. Both modifiers are primarily meant to alert the oncologist to either a lack of complete work-up (NOS) or lack of a standard diagnosis despite adequate work-up (NEC).

**Bone and Soft-Tissue Tumors**

WHO CNS5 attempts to align the classification of mesenchymal nomeningothelial tumors with the WHO classification of bone and soft-tissue tumors. Tumors that overlapped both classification systems but were rarely encountered in the CNS (eg, leiomyoma) were removed. Additionally, 3 newly recognized mesenchymal tumors were added to WHO CNS5: intracranial mesenchymal tumor, FET-CREB fusion-positive, CIC-rearranged sarcoma, and primary intracranial sarcoma, DICER1-mutant.

The following sections describe the WHO CNS5 newly described tumor types and are summarized in the Online Supplemental Data. For a general review of WHO CNS5, the readers are referred to an excellent review by Osborn et al.

**Diffuse Astrocytoma, MYB- or MYBL1-Altered**

This WHO grade 1 tumor is 1 of 4 low-grade pediatric tumors that require molecular differentiation from one another due to their similar, nonspecific, low-grade histologic characteristics. The defining feature of this tumor is structural variation, such as fusion, rearrangements, or amplification, involving MYB or MYBL1, which are transcriptional regulators for cellular proliferation and differentiation. IDH and H3 are wild-type by definition. The median age at diagnosis is 5 years (range, 0–26 years), and there is no sex predilection. Reflecting the histopathology, the imaging features are nonspecific but typical of a low-grade glioma with an infiltrative, heterogeneously T2-hyperintense, nonenhancing, non-diffusion-restricting mass. The cerebral cortex is the most common location, followed by supratentorial white matter/ deep gray nuclei, then the brainstem (Fig 1).

**Polymorphous Low-Grade Neuroepithelial Tumor of the Young**

Polymorphous low-grade neuroepithelial tumor of the young is another of the 4 types of pediatric low-grade tumors and is defined as WHO grade 1. It is a glial tumor with oligodendrogliotic features, frequent calcifications, and an infiltrative growth pattern. It is characterized by strong CD34 immunostaining and mitogen-activated protein kinase (MAPK) pathway alterations, specifically involving FGFR or BRAF. The most specific alteration appears to be FGFR2-CTNNA3 fusion. The median age at diagnosis is 15.5 years (range, 5–57 years), with a slight female predominance (male/female ratio, 1:1.7), and epilepsy is the most common presentation (87%). The tumor is located supratentorially, almost always cortically or subcortically, with two-thirds in the temporal lobe. Prominent dense calcifications are classic, with calcifications occurring in 83% of cases. Typical tumors are well-circumscribed, solid, and cystic, T1- and T2-signal variable, T2-FLAIR hyperintense, and nonenhancing or mildly enhancing (Fig 2).

**Diffuse Low-Grade Glioma, MAPK Pathway–Altered**

Diffuse low-grade glioma is another of the low-grade pediatric tumors. While not yet assigned a WHO grade, histologically, it behaves like a WHO grade 2 tumor with an oligodendroglial, astrocytic, or mixed pattern with infiltrative growth and typical low-grade cellular features. Numerous molecular alterations can activate the oncogenic MAPK pathway. More common alterations involve FGFR1 and BRAF; less common alterations involve NTRK1/2/3, MET, FGFR2, and MAP2K1. IDH1/2 and H3F3s mutations and CDKN2A homozygous deletions must be absent. This tumor commonly presents with epilepsy in the pediatric population and occasionally in adults. While there is a paucity of...
literature on the radiologic findings of this tumor, given its histopathologic similarity to the other pediatric low-grade tumors, it is presumed that the imaging findings are also similar. A T2-FLAIR and T2-hyperintense, nonenhancing, cortical, temporal lobe mass is demonstrated (Fig 3).

**Diffuse Hemispheric Glioma, H3 G34-Mutant**

Diffuse hemispheric glioma is a high-grade pediatric-type tumor, definitionally WHO grade 4.1,20 Histopathologic features are similar to those of either glioblastoma or what was previously called a primitive neuroectodermal tumor. The glioblastoma-type tumors are malignant, hypercellular gliomas with astrocytic differentiation, high mitotic rates, microvascular proliferation, and necrosis. The defining molecular feature of this tumor is a missense mutation of *H3F3a*, which codes for histone H3, causing arginine or less commonly valine to be substituted for the normal glycine 34 (when numbered using the legacy nomenclature, which does not include the initiating methionine in the numbering).1,20 There is a strong association with *ATRX* and *TP53* mutations. PDGFRA amplification is associated with the glioblastoma morphology. *CCND2* amplification is associated with the primitive neuroectodermal tumor morphology.1,20 The median age at diagnosis is 15.8 years (interquartile range, 13–22 years), with a slight male predominance (male/female ratio, 1.5:1).21 The frontal and parietal lobes are the most common locations with frequent abutment of leptomeningeal or ependymal surfaces. Margins may be sharp or ill-defined. Most tumors are hyperdense,
T1-hypointense, T2-hyperintense, enhancing, and diffusion-restricting. In adults, there may be no or only faint enhancement, in which case diffusion restriction is more helpful in assessing aggressiveness.22 Tumoral hemorrhage and necrosis can be seen and occasionally calcification (Fig 4).23

**Diffuse Pediatric-Type High-Grade Glioma, H3 Wild-Type and IDH Wild-Type**

Diffuse pediatric-type high-grade glioma is another of the 4 pediatric high-grade glioma types. It does not have an assigned WHO grade or a single defining molecular or genetic feature.2 About half of tumors previously classified as “pediatric glioblastoma” demonstrate mutations of histone 3 or uncommonly IDH1/2. The remaining heterogeneous tumors now fall under this new classification. The 3 recognized subtypes are characterized by MYCN, PDGFRα, and EGFR amplifications with numerous coexisting genetic abnormalities described.24 The MYCN subtype has high cellularity and mitosis, spindle, and epithelioid cell components; necrosis; and microvascular proliferation.2526 The median age at diagnosis is 8–11 years (range, 2–18 years).24 There is no sex predilection overall, but there is a slight male predominance for the EGFR subtype (male/female ratio, 1.6:1).24 The location is usually supratentorial, with the posterior fossa approaching 20% of cases, depending on subtype.24 The MYCN subtype classically shows a solid, enhancing, diffusion-restricting, well-marginated temporal lobe mass abutting the meninges with tumoral necrosis, rare hemorrhage, and no calcifications.2526 A tumor in the pons has greater enhancement and diffusion restriction compared with a diffuse midline glioma, H3 K27-altered.29 Figure 5 demonstrates a less-typical case without enhancement of the primary tumors.

**Infant-Type Hemispheric Glioma**

Infant-type hemispheric glioma is a pediatric-type, diffuse, high-grade glioma that has not yet been assigned a specific WHO grade.

The hallmark of this tumor is receptor tyrosine kinase gene fusions of ALK, ROS1, NTRK1/2/3, or MET.1 NTRK3 fusion has also been described in congenital mesoblastic nephroma and congenital fibrosarcoma, implying that such genetic alterations are tied to age-related mechanisms.27 Most of these tumors show high-grade histologic features.27 Histopathology shows hypercellularity, astrocytic differentiation, necrosis, microvascular proliferation, and nuclear pleomorphism.28 The median age at diagnosis is 2.8 months (range, 0.0–12.0 months) with no sex predilection. Overall median survival is 1.9 years.27 The tumors are almost always located in the cerebral hemispheres.27 Imaging data are scarce, but tumors tend to be large with solid and prominent cystic components, intratumoral hemorrhage, and enhancement.2931 Leptomeningeal disease has been reported.30

**High-Grade Astrocytoma with Piloid Features**

High-grade astrocytoma with piloid features is a circumscribed astrocytic glioma that has not yet been assigned a WHO grade but behaves like WHO grade 3 or 4.815 A hallmark of this tumor is its unique methylation profile.32 The most common genetic abnormalities are cdkn2A/B deletion, MAPK pathway alteration (affecting NF1, BRAF, and FGFR1), and ATRX mutation or loss of expression. Histologically, tumors tend to show moderate cellularity, glioblastoma-like foci, moderate nuclear pleomorphism, a moderate mitotic rate, lack of necrosis, vascular hypertrophy, and infiltrative growth.32 Most occur in the posterior fossa (74%), usually in the cerebellum, followed by supratentorial then spinal locations. The median age is 41.5 years, with occurrence from pediatrics to the elderly and no sex predilection.32 There appears to be an association with neurofibromatosis type 1.33 Tumors tend to be T1-hypointense-to-isointense, T2-hyperintense, heterogeneous enhancing, non-diffusion-restricting, and non-necrotic with sharp or ill-defined margins (Fig 6).12

**Diffuse Glioneuronal Tumor with Oligodendroglialike Features and Nuclear Clusters (Provisional Type)**

Diffuse glioneuronal tumor with oligodendroglialike features and nuclear clusters is a provisional tumor that has not yet been assigned a WHO grade. The hallmark of this tumor is its unique methylation profile.34 Additionally, monosomy 14 is seen in almost all cases. Histologically, the tumors tend to have oligodendroglialike perinuclear haloes, clear cell morphology, vascular growth, nuclear clusters resembling “pennies on a plate,” moderate-to-high cellularity, and infiltrative growth.34 Calculifications have been reported.35 The median age is 9 years (range, 2–75 years), and there is no sex predilection.34 Location is usually in the cerebral hemispheres, more commonly in the temporal lobe.34 A typical tumor is solid and cystic, T1-hypointense, T2-hyperintense, and...
nonenhancing-to-minimally enhancing with calcifications and without adjacent edema (Fig 7).35

**Myxoid Glioneuronal Tumor**

Myxoid glioneuronal tumor is a benign WHO grade 1 tumor that shows low-grade oligodendrocyte-like tumor cells with a myxoid-/mucin-rich stroma on histology. A fine capillary network is sometimes present along with neurocytic rosettes. Glial fibrillary acidic protein (GFAP) and OLG2 are positive. The defining feature is a PDGFRα p.K385 mutation. Abnormalities in FGFR1, IDH1/2, BRAF, MYB, and MYBL1 are absent.36,37 Data are limited, but in the largest described series, the median patient age was 23.6 years (range, 6–65 years) with no sex predilection.38 These tumors have a propensity for the septum pellucidum.36,38 A typical mass is well-defined, lobulated, T1-hypointense, T2-hyperintense, nonenhancing, non-diffusion-restricting, and without surrounding edema.36,39

**Supratentorial Ependymoma, YAP1 Fusion-Positive**

Supratentorial ependymomas, which are WHO grade 2 or 3, are associated with many different mutations with YAP1 fusions accounting for only 7% of all supratentorial ependymomas.30 Within this group, YAP1-MAML1, and YAP1-FAM11B fusions are common.45-48 Histologically, bipolar spindle cells with elongated processes are seen among blood vessels. Perivascular anuclear zones form perivascular pseudorosettes, and some cells have cytoplasmic vacuolization. Neoplastic nuclei are moderate in size and round to ovoid with speckled chromatin. Rosenthal fibers are seen in the zone surrounding the tumor.46,47 Irregular cells resembling tancytes are visualized. GFAP, S-100, and vimentin are positive.45-47 Data are limited, but the reported median age is 1.4 years (range, 0–51 years) with most patients younger than 4 years of age and almost all younger than 9 years of age. There is a female predominance (male/female ratio, 1:3).45 Location is

T2-FLAIR shows relative hypointensity centrally and hyperintensity peripherally (Fig 8). There is no elevated CBF. Larger lesions can appear L-shaped and have mass effect, which can mimic high-grade tumors.36-39

**Multinodular and Vacuolating Neuronal Tumor**

Most of the multinodular and vacuolating neuronal tumors are WHO grade 1 tumors that have a MAP2K1 mutation, but FGFR2-ZMYND11 translocations and BRAF, DEPC5, SMO, TP53, PIK3CA, and CIC mutations can also occur.16,40 Histologically, there are multiple, discrete, and coalescent nodules with immature neuronal cells and round vesicular nuclei. Pericellular eccentric vacuolization with prominent nuclei and eosinophilic cytoplasm are seen. There is no mitosis, perivascular lymphocytic infiltration, microcalcification, or oligodendrogialike cells. OLG2, α-internexin, and synaptophysin are positive.40 The median age is 41 years (range, 8–63 years), and there is a slight female predominance (male/female ratio, 1:1.4).41 The tumor presents as cluster of variably-sized nodules in the subcortical ribbon and superficial subcortical white matter following the gyral contour. The frontal then parietal, occipital, and temporal lobes are the most common locations.41,42 The tumors are T1 iso- to hypointense, T2-hyperintense, nonenhancing, non-diffusion-restricting, and without mass effect, calcification, hemorrhage, or surrounding edema (Fig 9).41-44

**FIG 4.** Diffuse hemispheric glioma, H3 G34-mutant. Multifocal masses are seen in the right temporal and parietal lobes. The temporal mass shows heterogeneously increased T2 signal (A), heterogeneous low T1 signal with a few foci of T1-hyperintense hemorrhage (B), and heterogenous enhancement (C, arrows). The parietal mass shows similar signal characteristics with heterogeneous T2-FLAIR hyperintensity (D), T1-hypointensity (E), and enhancement (F, arrows). The histologic section reveals an infiltrating glioma with astrocytic morphology (G). Glioma cells are positive for ATRX (H) and GFAP (I) stains and negative for IDH1 R132H and OLG2. There was a Ki-67 proliferation index of up to approximately 20%. This immunophenotype suggested a mutation of H3 G34, warranting further genomic evaluation. Next-generation sequencing revealed a somatic mutation in H3-3A (also known as H3F3A). Currently, there are no clinically approved therapies specifically targeting H3-3A mutations.
within the lateral ventricles or in the brain parenchyma adjacent to them. For extraventricular, supratentorial ependymomas in general, the frontal and temporal lobes are the most common locations. A typical tumor is mixed density, solid and cystic, well-marginated, T1 iso- to hypointense, T2 iso- to hyperintense, enhancing, and diffusion-restricting with calcifications. Internal hemorrhage can occur.

### Posterior Fossa Ependymoma, Group PFA

Posterior fossa ependymomas are divided into groups PFA and PFB. PFA is a WHO grade 2 or 3 tumor characterized by loss of H3 K27 trimethylation due to *EZHIP* overexpression. PFA tumors are further divided into PFA-1 and PFA-2 based on the specific mutation present. PFA-1 has *HOX* mutations while PFA-2 has *EN2* and *CNPY1* mutations. Histology demonstrates well-differentiated cells with ependymal rosettes and perivascular pseudorosettes. Dystrophic calcification, hemorrhage, myxoid degeneration, and metaplasia can also be seen. GFAP and S-100 are positive, and OLIG2 is negative. The median age is 3 years (range, 0–51 years) with most patients younger than 9 years of age. Overall survival at 5 and 10 years of age is 68% and 56%, respectively. PFAs account for nearly 90% of all posterior fossa ependymomas. Tumors arise from the roof of the fourth ventricle or the cerebellopontine cistern, can traverse the foramina of Luschka or Magendie, and can encase cranial nerves and vessels. The typical imaging appearance shows calcification, cystic change, T1 iso- to hypointensity, T2-hyperintensity, and heterogeneous enhancement. Hemorrhage and diffusion restriction can be present.

### Posterior Fossa Ependymoma, Group PFB

PFB is a WHO grade 2 or 3 tumor characterized by increased H3 K27 trimethylation. PFB ependymomas also arise from the fourth ventricle but more commonly from the floor as opposed to the roof. In comparison with PFA, PFB...
tumors more commonly occur in adolescents and young adults. On the basis of supplemental data from the largest reported series, the overall median age is 27.5 years (range, 1–72 years) with no sex predilection, though there are age and sex differences among PFB subtypes. Prognosis is substantially better than for PFA, with overall survival at 5 and 10 years being 100% and 88%, respectively. The histology and immunohistochemistry findings are similar to those of PFA. The imaging findings are also similar; however, compared with PFA tumors, PFB tumors tended to be more cystic, less calcified, and less enhancing.

**Spinal Ependymoma, MYCN-Amplified**

Spinal ependymoma is a rare, aggressive tumor of the spinal cord. While not yet assigned a specific WHO grade, its histologic features are usually WHO grade 3 but can be WHO grade 2. Its defining feature is amplification of MYCN, which has been implicated as
the driver of its aggressive behavior. Histologically, this tumor is anaplastic with marked cellular atypia and nuclear hyperchromasia. Prominent pink nucleoli, necrosis, mitosis, and glomeruloid vascular proliferation are common. GFAP and EMA are positive. While data are limited, the reported median age is 32 years (range, 12–56 years) with no sex predilection. These tumors can grow to be large and cause spinal canal widening. A typical tumor is well-demarcated, iso- to hyperdense, T1 iso- to hypointense, and T2 iso- to hyperintense. Enhancement is variable. A hemosiderin rim (“cap sign”) may form from tumoral hemorrhage.

**Cribriform Neuroepithelial Tumor (Provisional Type)**

Cribriform neuroepithelial tumor is a benign tumor that has not yet been assigned a WHO grade. It is defined by a large, heterozygous deletion in *SMARCB1*, which is also seen in atypical teratoid/rhabdoid tumor (AT/RT). The key histologic features of cribriform neuroepithelial tumor are the presence of cribriform strands, ribbons, and nuclei with dense chromatin. Cells lack prominent nucleoli, and the cytoplasm is slightly eosinophilic and ill-defined. In more compact areas, small lumina may be seen with true rosettes. Tyrosinase, EMA, vimentin, MAP2C, and synaptophysin are positive. While data are limited, the reported median age is 1.7 years (range, 0.8–10.8 years) without a definite sex predilection. The location is intraventricular or within the brain parenchyma adjacent to the
ventricles. Tumors have been described in the lateral, third, and fourth ventricular regions without a clear predilection for 1 of these 3 locations. Imaging typically reveals a large mass with T1-hypointensity, T2-hyperintensity, heterogeneous enhancement, and diffusion restriction.

CNS Neuroblastoma, FOXR2-Activated

CNS neuroblastoma is a highly malignant embryonal tumor without an official WHO grade. These tumors have variable chromosomal rearrangements or mitochondrial DNA insertions converging on FOXR2, leading to overexpression. FOXR2 binds to and stabilizes MYC and MYCN proteins and therefore promotes MYC-related transcriptional activities, leading to increased cellular proliferation and tumorigenesis. Histology shows a small-cell tumor, embryonal architecture, a high proportion of neuropil, neurocytic cell, or ganglion cell differentiation, and, frequently, vascular pseudorosettes and nuclear palisades. OLIG2 and synaptophysin are positive. The median age is 4.5 years (range, 1.4–16 years) without a sex predominance (male/female ratio, 1:2.3). Location can be supratentorial or infratentorial, but dural abutment is common. A typical tumor is large, solid, centrally necrotic, iso- to hypodense, T2-hyperintense, diffusion-restricting, and mildly enhancing. Calcification or blood products are sometimes present at the border of the necrotic region. Large intratumoral macroscopic vessels may be present (Fig 11).

Desmoplastic Myxoid Tumor of the Pineal Region, SMARCB1-Mutant

Desmoplastic myxoid tumor is a tumor of the pineal region without a specific WHO grade that has a mutation in SMARCB1, resulting in a loss of function, similar to AT/RT. Histologically, there is no brisk mitotic activity or necrosis, typically seen in AT/RT. These tumors have a variable myxoid morphology combined with spindled and epithelioid cells embedded within a densely collagenized stroma. CD34 is positive, and INI1 is negative. Unlike AT/RT, this tumor more commonly occurs in adults (median age, 40 years; range, 15–61 years). Data are limited, but the reported median age is 1.8 years (range, 1.2–7.6 years) with a female predominance (male/female ratio, 1:2.3). Location can be supratentorial or infratentorial, but dural abutment is common. A typical tumor is large, solid, centrally necrotic, iso- to hypodense, T2-hyperintense, diffusion-restricting, and mildly enhancing. Calcification or blood products are sometimes present at the border of the necrotic region. Large intratumoral macroscopic vessels may be present (Fig 11).
but there does not appear to be a sex predilection. On imaging, there is variable T1 signal, T2 intermediate signal, and enhancement. Large tumors can compress the cerebral aqueduct and cause obstructive hydrocephalus.

**Intracranial Mesenchymal Tumor, FET-CREB Fusion-Positive (Provisional Type)**

Intracranial mesenchymal tumor is a group of rare mesenchymal CNS tumors without an assigned WHO grade. Intracranial angiomatoid fibrous histiocytomas and intracranial myxoid mesenchymal tumors have now been combined into this group because both have an in-frame genetic fusion of a FET RNA-binding protein (EWSR1 or FUS) to a CREB transcription factor (ATF1, CREB1, or CREM). Histology is variable and may show solid nodules of epithelioid or spindled cells with a syncytial growth pattern, pseudoangiomatous spaces, a fibrous pseudocapsule, prominent pericapsular lymphoplasmacytic infiltrates, or mucin-rich stroma. Desmin, CD99, and EMA are positive, and skeletal and smooth muscle markers, S-100, GFAP, and OLIG2 are negative. The median age is 17 years (range, 4–70 years) with a female predominance (male/female ratio, 1:2.2). Location is typically extra-axial, most commonly along the cerebral convexities but can be intraventricular or infratentorial. A dural tail and calvarial involvement may be present. A typical tumor is well-circumscribed, lobulated, and cystic and solid with T2 and T2-FLAIR hyperintensity and enhancement. Internal blood products may be present. Extensive adjacent vasogenic edema is common (Fig 12).15

**CIC-Rearranged Sarcoma**

CIC-rearranged sarcoma is a highly aggressive WHO grade 4 round cell mesenchymal neoplasm that is one of the most common and best characterized subgroups of “Ewing-like sarcomas” and is predominantly extraskeletal. These tumors are characterized by CIC rearrangements with multiple fusion partners identified (DUX4, FOXO4, LEUTX, NUTM1, NUTM2A). The CIC-NUTM1 fusion pair appears to have a greater predilection for the CNS. Histologically, they are small, round cell tumors, but in contrast to Ewing sarcoma, they exhibit distinctive nucleoli in cells with vesicular nuclei, variable epithelioid morphology occasionally with clear cytoplasm, focal myxoid change and cell spindling, and reduced uniformity of nuclei size and shape. CD99, ETV4, and WT1 are positive. Data are limited for CIC-rearranged sarcoma of the CNS, but cases have been reported in both pediatric and adult patients. Location is anywhere along the neuroaxis. A typical tumor is extra-axial, solid, variably lobulated; T2 iso- to hyperintense; and homogeneously or heterogeneously enhancing (Fig 13). Peritumoral edema can be present.

**Primary Intracranial Sarcoma, DICER1-Mutant**

Primary intracranial sarcoma is a highly malignant tumor, associated with familial DICER1 syndrome and occasionally neurofibromatosis type 1. A specific WHO grade has not yet been assigned. There are several other DICER1-associated tumors in and outside the CNS. The DICER1 encodes a protein that facilitates activation of an RNA-induced silencing complex. Disruption of this pathway leads to altered protein expression, activation of the NRAS variants, inactivation of TP53, and copy number alternations. Histologically, there is high cellularity, brisk mitotic activity, intratumoral hemorrhage, some areas of fascicular spindle cells, and embryonic-type tissues, which may have rhabdomyoblastic differentiation. Coalescence of cells into “organoid” formations has been observed. PAS, α-1 antitrypsin, and desmin are positive, with patchy-to-complete loss of H3K27me. The median age is 6.0 years (range, 2.0–17.5 years) without a sex predilection. Tumors are presumed to arise from mesenchymal progenitor cells located within the

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**FIG 12.** Intracranial mesenchymal tumor, FET-CREB fusion–positive (provisional type). Sagittal (A–C) and axial (D–F) MR images demonstrate a lobulated circumscribed mass along the superior vermis. The mass is markedly T2-FLAIR hypointense (A and D), T1-hypointense (B), homogeneously enhancing (C), and T2-hyperintense (E), with marked surrounding vasogenic edema. There is a lack of hypointensity within the tumor on the susceptibility-weighted image (F). Histology demonstrates a mesenchymal neoplasm with low-grade features (G), with staining positive for reticulin (H) and desmin (I), markers of connective tissue and muscle, respectively. The marked T2-FLAIR hypointensity corresponding to the area of homogeneous enhancement is an atypical appearance.
meninges or perivascular spaces\textsuperscript{83} and thus can present as intraxial or extra-axial masses. Intra-axial masses tend to be peripheral and within the cerebral hemispheres.\textsuperscript{82,86} The typical appearance is hyperdense, T2 iso- to hypointense, diffusion-restricting, and enhancing, with intratumoral hemorrhage and peritumoral edema.\textsuperscript{82,85,87}

**Pituitary Blastoma**

Pituitary blastomas are rare WHO grade 4 embryonal tumors of the adenohypophysis associated with \textit{Dicer1} mutations.\textsuperscript{15,83,88} Histologically, these tumors resemble the embryonic pituitary gland and are composed of blastema-like cells, epithelial glands with rosettes resembling primitive Rathke-type epithelia, and large secretory epithelial cells that express hormones such as adrenocorticotropic hormone or rarely growth hormone.\textsuperscript{85,89} In the largest reported series, the median age was 11 months (range, 2–24 months) with a slight female preclusion (male/female ratio, 1:1.4),\textsuperscript{89} though a case in a young adult has been described.\textsuperscript{89} The most common clinical presentation is an infant with Cushing syndrome, ophthalmoplegia, and/or diabetes insipidus.\textsuperscript{85} The imaging appearance is variable, ranging from a small pituitary mass to a large heterogeneous solid and cystic mass mimicking a macroadenoma.\textsuperscript{89} Internal calcification has been reported in 1 case.\textsuperscript{89}

**CONCLUSIONS**

The 2021 version of the WHO CNS tumor classification includes terminology updates reflecting more accurate understanding of tumorigenesis as well as the presentation of 22 newly recognized tumors, which were reviewed here. This edition furthers the growing movement away from purely histologic diagnoses and toward molecular diagnoses, increasing the emphasis on specific genetic mutations and DNA methylation-based classification. Because this classification system improves standardization in diagnosis and facilitates targeted treatments, it will continue to grow and adapt on the basis of new understanding of molecular alterations and tumor pathogenesis.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Stent-Assisted Coiling in the Treatment of Unruptured Intracranial Aneurysms: A Randomized Clinical Trial


ABSTRACT

BACKGROUND AND PURPOSE: Stent-assisted coiling may improve angiographic results of endovascular treatment of unruptured intracranial aneurysms compared with coiling alone, but this has never been shown in a randomized trial.

MATERIALS AND METHODS: The Stenting in the Treatment of Aneurysm Trial was an investigator-led, parallel, randomized ([1:1] trial conducted in 4 university hospitals. Patients with intracranial aneurysms at risk of recurrence, defined as large aneurysms (≥10 mm), postcoiling recurrent aneurysms, or small aneurysms with a wide neck (≥4 mm), were randomly allocated to stent-assisted coiling or coiling alone. The composite primary efficacy outcome was “treatment failure,” defined as initial failure to treat the aneurysm; aneurysm rupture or retreatment during follow-up; death or dependency (mRS > 2); or an angiographic residual aneurysm adjudicated by an independent core laboratory at 12 months. The primary hypothesis (revised for slow accrual) was that stent-assisted coiling would decrease treatment failures from 33% to 15%, requiring 200 patients. Primary analyses were intent to treat.

RESULTS: Of 205 patients recruited between 2011 and 2021, ninety-four were allocated to stent-assisted coiling and 111 to coiling alone. The primary outcome, ascertainable in 203 patients, was reached in 28/93 patients allocated to stent-assisted coiling (30.1%; 95% CI, 21.2%–40.6%) compared with 30/110 (27.3%; 95% CI, 19.4%–36.7%) allocated to coiling alone (relative risk = 1.10; 95% CI, 0.7–1.7; P = .66). Poor clinical outcomes (mRS ≥2) occurred in 8/94 patients allocated to stent-assisted coiling (8.5%; 95% CI, 4.0%–16.6%) compared with 6/111 (5.4%; 95% CI, 2.2%–11.9%) allocated to coiling alone (relative risk = 1.6; 95% CI, 0.6%–4.4%; P = .38).

CONCLUSIONS: The STAT trial did not show stent-assisted coiling to be superior to coiling alone for wide-neck, large, or recurrent unruptured aneurysms.

ABBREVIATIONS: CA = coiling alone; DSMC = Data and Safety Monitoring Committee; RR = relative risk; SAC = stent-assisted coiling; UIA = unruptured intracranial aneurysm.
multiple case series and meta-analyses published during 20 years. A randomized trial comparing the results of coiling with or without stent placement has never been published.

The Stenting in the Treatment of Aneurysm Trial (STAT) was launched in 2011 to provide a clinical research context for the use of SAC in UIAs. The trial compared a policy of coiling alone (CA) versus the use of a self-expandable stent (any stent, not a flow diverter) in addition to the coiling procedure. The primary hypothesis of the trial was that in patients with aneurysms prone to recurrence, SAC would decrease the proportion of patients reaching "treatment failure," a composite clinical and angiographic primary outcome measure that included aneurysmal rupture or retreatment during follow-up or a recurrent or residual aneurysm on follow-up angiography at 12 months. We here report the final results of the trial.

MATERIALS AND METHODS
This report follows the Consolidated Standards of Reporting Trials (CONSORT) recommendations. STAT was an investigator-led, multicenter randomized controlled trial integrated into clinical practice. The trial proposed randomized allocation to SAC or CA in patients eligible for both options. There were 4 participating centers (Montreal, Ottawa, and Edmonton in Canada, and Brest in France). All sites received institutional review board approval. The protocol was published, and the trial was registered at http://www.clinicaltrials.gov number NCT01340612.

Patients
All patients were 18 years of age or older with a life expectancy of at least 2 years. Patients had at least 1 UIA prone to recurrence, defined and categorized at the time of registration before randomization as a large (≥10 mm) aneurysm (STAT-1), a recurrent aneurysm after previous coiling (STAT-2), or a wide-neck (≥4 mm) aneurysm of <10 mm (STAT-3). There were few exclusion criteria: 1) absolute contraindications to endovascular treatment, anesthesiia, or the use of dual antiplatelet regimens; 2) the presence of other aneurysms requiring treatment during the same session; 3) the presence of an associated cerebral arteriovenous malformation; 4) recently ruptured aneurysms (<3 months); and 5) the presence of a recurring, previously stented aneurysm. Screening logs of all potentially eligible patients with UIAs were not required per protocol. All patients signed an informed consent form.

Randomisation and Masking
SAC or CA was randomly allocated (1:1) using a Web-based platform assuring concealment of the allocation. The randomized allocation was stratified according to the STAT1–3 subgroups and minimized for the type of coils to be used (platinum or second generation). Patients, interventionists, and outcome assessors were not blinded to treatment assignment.

Interventions and Follow-up Tests and Visits
Coiling with or without stent placement was performed according to standards of practice, with the patient under general anesthesia. Antiplatelet and anticoagulation regimens and testing for platelet inhibition were prescribed according to routine practice at each site. Details regarding the endovascular technique; type of coils; use of adjunctive techniques such as balloon remodeling (routine in STAT centers for large or wide-neck aneurysms); whether the stent was deployed before or following coiling; the use of multiple stents; and posttreatment medical management decisions were left to the discretion of the treating physicians. A stent could be used as a bailout maneuver in patients allocated to CA if this was judged appropriate by the treating physician, to ensure the safety of patients. Similarly, the physician could choose not to use the stent in patients allocated to SAC when it was judged impossible or dangerous at the time of the procedure.

Follow-up tests and visits were limited to those considered clinically indicated, such as neurologic examinations, brain imaging studies, and a functional assessment according to the mRS score at discharge, 1 month, and 12 (±3) months. Follow-up angiography (invasive or noninvasive) at 12 (±3) months was considered standard of practice.

Data capture and management through secure servers (MedSciNet; https://medscinet.com/about.aspx) were in compliance with good clinical practice requirements. Case report forms were simple, and the data collected were parsimonious, to facilitate completion by care personnel, because no financial compensation was provided to participating centers.

Primary and Secondary Outcome Measures
The primary end point of the 2011 protocol was the incidence of angiographic recurrences at 12 (±3) months, defined as the following: 1) an angiographic recurrence of the lesion, as judged by an independent core lab (composed of 2 raters) according to a previously published classification; 2) an episode of intracranial bleeding; or 3) retreatment of the same lesion by endovascular or surgical means during the follow-up period. Furthermore, the protocol stipulated that "recurrences would be recorded (present or absent) as they are discovered, at the follow-up assessment (12 ± 3 months), as clinical symptoms appear at any time, or at time of death." Because this definition lacked precision and may not be ascertainable in some patients, the primary outcome was modified in July 2021, after consulting with the Data and Safety Monitoring Committee (DSMC) but before any data examination, to be in line with other endovascular trials. Two other components have been added to the composite primary outcome, treatment failure (initial treatment failure using any device and treatment-related death or dependency precluding follow-up angiography). If the coiling procedure was not feasible, for example due to coil instability, the physician had the option of using a stent, a use that was not considered a failure of the initial treatment (but was counted as a crossover in "as-treated analyses"). One primary poor outcome was attributed per patient. When a patient met >1 of the criteria, the following hierarchical order was prespecified to classify the patient for final analyses: death or mRS 3–5 (from any cause within 30 days of the intervention and from related causes during follow-up) > aneurysm rupture during follow-up > retreatment during follow-up > initial treatment failure (defined as the inability to perform endovascular treatment) > major recurrence or residual aneurysm at imaging follow-up (3–12 months) as adjudicated by an independent core
laboratory of 2 neuroradiologists blinded to treatment groups and according to a previously validated classification.25,26

Secondary outcomes included the individual components of the composite primary outcome: the mRS score at discharge and 12 months posttreatment; the success in occluding the aneurysm at the end of the procedure; perioperative complications (ischemic strokes and intracranial hemorrhages within 31 days of the intervention and during follow-up); angiographic results at 12 months; length of hospital stay (number of days); discharge disposition (home, other hospital, rehabilitation facility; death); and retreatment of the index aneurysm at any time.

Hypotheses and Number of Patients
The 2011 protocol planned for the recruitment of 600 patients.19 This number was based on 2 hypotheses: The primary efficacy hypothesis was that SAC would decrease angiographic recurrences by 20% at 12 months and a total sample size of 536 patients would allow the detection of such a difference with a power of 80% and an error of 0.0125 (to account for subgroup analyses for the 3 main categories of lesions: large, wide neck, and recurrent aneurysms). The secondary safety hypothesis was that the use of intracranial stent placement would not double the number of dead or dependent patients (mRS > 2) from 6% to 12% at 12 months. In July 2021, before any knowledge of the data, the steering committee (SC), in agreement with the DSMC, dropped the safety hypothesis and modified the primary efficacy hypothesis: SAC was hypothesized to decrease treatment failures from 33% to 15%, which would require approximately 200 patients (88 patients per group; power of 80% and α of 5%, plus 10% to account for crossovers and losses to follow-up). Details are provided in the Online Supplemental Data.

Trial Interruption
On August 31, 2021, after a blinded examination of interim results, the DSMC recommended trial continuation. However, in September 2021, ten years after the recruitment of the first patient, the SC decided to finalize and report the trial.

Statistical Analyses
Blinded data were examined at prespecified intervals by an independent DSMC, composed of an interventional neurologist, a dual-trained neurosurgeon, and a statistician; but no hypothesis testing was performed.

Descriptive statistics on demographic variables and preoperative data are provided to compare the 2 groups at baseline. Means, SDs, medians, and ranges are presented for quantitative variables, and frequency tables for categoric variables. Primary safety and efficacy outcomes are described using percentages and 95% CIs. The intent-to-treat analyses for the primary efficacy hypothesis were performed on available observations. The relative risks (RRs and 95% CIs) were estimated using a generalized estimating equation with a binomial distribution and a log-link function. The groups were not different with respect to risk factors for poor outcomes, and no adjustments for residual confounding factors were made.

The analyses of interaction between prespecified subgroups of interest and treatment were made by adding subgroup variables and interaction in generalized estimating equation models. Patient and aneurysm subgroups were examined as prespecified in 2011, regardless of the results of tests for interaction. Subgroup results according to STAT 1–3 categories indicated at the time of registration, according to aneurysm size (<10 mm or ≥10 mm), neck size (<4 mm or ≥4 mm), and location (posterior circulation and anterior circulation subdivided into carotid, anterior cerebral artery, and MCA aneurysms) are reported. As-treated exploratory analyses (defined as coiling with or without any attempt or use of stent placement, regardless of treatment allocation) are also provided. We also explored what results would have been if complete occlusion (rather than the combination of complete and near-complete occlusion) had been used as the criterion for a good angiographic outcome. One adverse event is reported per patient. When a patient had >1 event, we used the most severe to categorize the patient. Analyses were performed using SAS software, Version 9.4 (SAS Institute) and SPSS, Version 26 (IBM) with a significance level of 5%.

Roles of the Sponsor and Funding Source
The trial was sponsored by the Center Hospitalier de l’Université de Montréal. The sponsor had no part in the study design, data collection, analysis, or reporting and no access to the data or source documents. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication. There was no funding source for this study.

RESULTS
Between August 2011 and August 2021, we recruited 205 patients: Ninety-four were assigned to SAC, and 111 to CA. For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome is illustrated in the trial profile (Fig 1).

The baseline patient and aneurysm characteristics are shown in Table 1. Groups were comparable: Ninety-two (44.9%) patients had small wide-neck aneurysms (STAT-3); 75 (36.6%), a recurrent
aneurysm (STAT-2); and 38 (18.5%), a large aneurysm (STAT-1). The most frequent locations were the anterior communicating artery (65; 31.7%), basilar bifurcation (47; 22.9%), and MCA bifurcation (32; 15.6%).

Seventeen of 111 patients (15.3%) allocated to CA underwent SAC, while 10/94 (10.6%) patients allocated to SAC were treated with CA. Technical details regarding treatment for both groups are provided in the Online Supplemental Data. In 4 patients from STAT-2, residual aneurysms were judged too small for any treatment (3 in the SAC arm and 1 in the CA arm). Seven patients were treated with flow diverters (3 in the SAC arm and 4 in the CA arm). Patients allocated to SAC were initially treated with a single ($n = 64$) or 2 ($n = 14$) stents. Stents were delivered before coiling in 20/78 (25.6%) and after coiling in 58/78 (74.4%) patients.

The primary outcome is available for 203/205 patients (99%), with 1 patient missing in each group (Fig 1 and Tables 2 and 3). Treatment failure occurred in 28/93 patients allocated to SAC (30.1%; 95% CI, 21.2%–40.6%) compared with 30/110 (27.3%; 95% CI, 19.4%–36.7%) allocated to CA $(RR = 1.10; 95\% \text{ CI}, 0.7$–$1.7; P = .66)$. Details of each component of the primary outcome in the intent to treat analysis are provided in Table 2.

There were no incidences of aneurysm rupture during follow-up. Three patients were retreated (all in the SAC group). Angiographic results at 12 months accounted for most of the primary outcome adjudications (185/203; 91%). Follow-up vascular imaging studies, available in 198 patients (96.6%), were performed by MRA in 135 (68.2%), by catheter angiography in 59 (29.8%), and by CTA in 4 (2%) patients. More patients were followed by catheter angiography in the SAC group (37.2%) than in the CA group (21.6%) (Table 3). The mean time of angiographic follow-up was 14.8 (SD, 9.5) months for patients allocated to SAC, and 13.5 (SD, 5.2) months for patients allocated to CA. The mean time of the follow-up mRS evaluation was 15.3 (SD, 8.0) months for SAC and 15.7 (SD, 10.5) months for CA.

Results for predefined subgroups of interest are illustrated in the forest plot (Fig 2), even though none of the interaction tests were significant.

### Table 1: Patient and index aneurysm characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CA ($n = 111$)</th>
<th>SAC ($n = 94$)</th>
<th>Total ($n = 205$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at treatment (mean) (SD) (yr)</td>
<td>58.6 (10.4)</td>
<td>58.0 (8.8)</td>
<td>58.3 (9.7)</td>
</tr>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (No.) (%)</td>
<td>77 (69.4)</td>
<td>65 (69.1)</td>
<td>142 (69.3)</td>
</tr>
<tr>
<td>STAT type lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAT-1: unruptured aneurysm, never treated,</td>
<td>21 (18.9)</td>
<td>17 (18.1)</td>
<td>38 (18.5)</td>
</tr>
<tr>
<td>with a dimension of $\geq 10$ mm (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAT-2: major recurrent aneurysm after</td>
<td>41 (36.9)</td>
<td>34 (36.2)</td>
<td>75 (36.6)</td>
</tr>
<tr>
<td>previous coiling, but no previous stent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placement (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAT-3: small (&lt;10 mm), wide-neck ($\geq 4$</td>
<td>49 (44.1)</td>
<td>43 (45.7)</td>
<td>92 (44.9)</td>
</tr>
<tr>
<td>mm aneurysm (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment mRS score (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>84 (75.7)</td>
<td>70 (74.5)</td>
<td>154 (75.1)</td>
</tr>
<tr>
<td>1</td>
<td>21 (18.9)</td>
<td>20 (21.3)</td>
<td>41 (20.0)</td>
</tr>
<tr>
<td>2</td>
<td>5 (4.5)</td>
<td>2 (2.1)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.9)</td>
<td>1 (1.1)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1 (1.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>4 (3.6)</td>
<td>4 (4.3)</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>Additional aneurysm to a previously</td>
<td>13 (11.7)</td>
<td>6 (6.4)</td>
<td>19 (9.3)</td>
</tr>
<tr>
<td>ruptured and treated one</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental finding</td>
<td>94 (84.7)</td>
<td>84 (89.4)</td>
<td>178 (86.8)</td>
</tr>
<tr>
<td>Index aneurysm location (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>78 (70.3)</td>
<td>58 (61.7)</td>
<td>136 (66.3)</td>
</tr>
<tr>
<td>Ophthalmic/paroophthalmic</td>
<td>7 (6.3)</td>
<td>3 (3.2)</td>
<td>10 (4.9)</td>
</tr>
<tr>
<td>Posterior communicating/anterior choroidal</td>
<td>7 (6.3)</td>
<td>13 (13.8)</td>
<td>20 (9.8)</td>
</tr>
<tr>
<td>Carotid terminus</td>
<td>6 (5.4)</td>
<td>1 (1.1)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>MCA bifurcation/M1</td>
<td>18 (16.2)</td>
<td>14 (14.9)</td>
<td>32 (15.6)</td>
</tr>
<tr>
<td>Anterior communicating/A1</td>
<td>40 (36.0)</td>
<td>25 (26.6)</td>
<td>65 (31.7)</td>
</tr>
<tr>
<td>Distal ACA</td>
<td>0</td>
<td>2 (2.1)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>33 (29.7)</td>
<td>36 (38.3)</td>
<td>69 (33.7)</td>
</tr>
<tr>
<td>PCA</td>
<td>0</td>
<td>3 (3.2)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Basilar terminus</td>
<td>24 (21.6)</td>
<td>23 (24.5)</td>
<td>47 (22.9)</td>
</tr>
<tr>
<td>SCA</td>
<td>3 (2.7)</td>
<td>5 (5.3)</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>Basilar trunk</td>
<td>2 (1.8)</td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Verteobasilar junction</td>
<td>1 (0.9)</td>
<td>2 (2.1)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>PCA</td>
<td>2 (1.8)</td>
<td>3 (3.2)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Index aneurysm maximal external size (mean)</td>
<td>9.2 (6.4)</td>
<td>9.2 (5.9)</td>
<td>9.2 (6.3)</td>
</tr>
<tr>
<td>(SD) (range) (mm)</td>
<td>(2–50)</td>
<td>(3–35)</td>
<td>(2–50)</td>
</tr>
<tr>
<td>$&lt;10$ (No.) (%)</td>
<td>74 (66.7)</td>
<td>63 (67.0)</td>
<td>137 (66.8)</td>
</tr>
<tr>
<td>$\geq 10$ (No.) (%)</td>
<td>37 (33.3)</td>
<td>31 (33.0)</td>
<td>68 (33.2)</td>
</tr>
<tr>
<td>Index aneurysm neck size (mean) (SD) (range)</td>
<td>4.4 (2.2)</td>
<td>4.1 (1.6)</td>
<td>4.3 (1.9)</td>
</tr>
<tr>
<td>(mm)</td>
<td>(2–20)</td>
<td>(2–9)</td>
<td>(2–20)</td>
</tr>
<tr>
<td>Aneurysm neck $\geq 4$ mm (No.) (%)</td>
<td>72 (64.9)</td>
<td>58 (61.7)</td>
<td>130 (63.4)</td>
</tr>
</tbody>
</table>

**Note:**—ACA indicates anterior cerebral artery; PCA, posterior cerebral artery; SCA, superior cerebellar artery.
Poor clinical outcomes (mRS > 2) in the intent to treat analysis are detailed in Table 4. A poor clinical outcome (mRS > 2) occurred in 8/94 patients allocated to SAC (8.5%; 95% CI, 4.0%–16.6%) compared with 6/111 (5.4%; 95% CI, 2.2%–11.9%) with CA (RR = 1.6; 95% CI, 0.6–4.4; \( P = .38 \)). Five deaths were related to treatment complications (2 in the CA and 3 in the SAC arms). Deaths unrelated to the aneurysm or treatment (and not included in the primary outcome measure) were reported in 3 patients (1 in the CA and 2 in the SAC groups). Details of poor clinical outcomes at any time point are provided in the Online Supplemental Data.

Adverse events occurred in 25/94 (26.6%) patients with SAC and 23/111 (20.7%) with CA (RR = 1.28; 95% CI, 0.78–2.11; \( P = .323 \)). Cerebrovascular ischemic and hemorrhagic events occurred in 21/94 (22.3%) patients with SAC, and in 18/111 (16.2%) with CA (RR = 1.38; 95% CI, 0.78–2.43; \( P = .268 \)). Complication rates according to subgroups of interest are provided in the Online Supplemental Data. The test of interaction was significant for aneurysm size (\( P = .02 \)): complications were more frequent in patient with aneurysms >10 mm allocated to SAC than in those allocated to CA (RR 2.0 ± 0.69 95% CI 1.0–3.9; \( P = .04 \)).

### Table 2: Primary outcome in intent-to-treat analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CA (n = 111)</th>
<th>SAC (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>30 (27.3)</td>
<td>28 (30.1)</td>
</tr>
<tr>
<td>Clinical</td>
<td>2 (1.8)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>mRS 6</td>
<td>2 (1.8)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>mRS 3–5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retreatment</td>
<td>0</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Angiographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate failure</td>
<td>3 (2.7)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Residual aneurysm (core lab)</td>
<td>22 (19.8)</td>
<td>18 (19.4)</td>
</tr>
<tr>
<td>Missing primary outcome</td>
<td>1 (0.9)</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

*RR = 1.10; 95% CI, 0.71–1.71; \( P = .656 \).*

### Table 3: Secondary outcomes in intent-to-treat analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CA (n = 111)</th>
<th>SAC (n = 94)</th>
<th>RR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td>0.78 (0.48–1.28)</td>
<td>.325</td>
</tr>
<tr>
<td>Patients hospitalized for &gt;3 days</td>
<td>30 (27.3)</td>
<td>20 (21.3)</td>
<td>1.18 (0.35–3.96)</td>
<td>.788</td>
</tr>
<tr>
<td>Discharge location</td>
<td></td>
<td></td>
<td>1.17 (0.43–3.22)</td>
<td>.761</td>
</tr>
<tr>
<td>Home</td>
<td>106 (95.5)</td>
<td>89 (94.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other than home</td>
<td>5 (4.5)</td>
<td>5 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other hospital</td>
<td>1 (0.9)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehabilitation center</td>
<td>2 (1.8)</td>
<td>2 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (1.8)</td>
<td>3 (3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS at discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>84 (75.7)</td>
<td>69 (73.4)</td>
<td>1.17 (0.43–3.22)</td>
<td>.761</td>
</tr>
<tr>
<td>1</td>
<td>17 (15.3)</td>
<td>16 (17.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7 (6.4)</td>
<td>7 (7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (1.8)</td>
<td>1 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2 (1.8)</td>
<td>3 (3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Year mRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>66 (60.0)</td>
<td>54 (57.4)</td>
<td>0.97 (0.42–2.23)</td>
<td>.936</td>
</tr>
<tr>
<td>1</td>
<td>30 (27.3)</td>
<td>26 (27.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7 (6.4)</td>
<td>7 (7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (1.8)</td>
<td>1 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3 (2.7)</td>
<td>5 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing mRS data</td>
<td>1 (0.9)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of 1-year mRS assessment (mean) (SD) (mo)</td>
<td>15.7 (10.5)</td>
<td>15.3 (8.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidity and mortality at 1 year (mRS &gt; 2), (No.)</td>
<td>6 (5.4%)</td>
<td>8 (8.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retreatment of index aneurysm during follow-up (No.)</td>
<td>0</td>
<td>3 (3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate angiographic outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete occlusion (No.)</td>
<td>67 (60.4)</td>
<td>55 (58.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual neck (No.)</td>
<td>33 (29.7)</td>
<td>30 (31.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual saccular aneurysm (No.)</td>
<td>11 (9.9)</td>
<td>9 (9.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic outcome at 1 year (core lab) (Detailed results in Online Supplemental Data)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete occlusion (No.)</td>
<td>38 (34.2)</td>
<td>42 (44.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual neck (No.)</td>
<td>43 (38.7)</td>
<td>24 (25.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual saccular aneurysm (No.)</td>
<td>27 (24.3)</td>
<td>24 (25.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year imaging not available* (No.)</td>
<td>3 (2.7)</td>
<td>4 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of 1-year imaging assessment (mean) (SD) (mo)</td>
<td>13.5 (5.2)</td>
<td>14.8 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up vascular imaging* (No.)</td>
<td>108 (97.3)</td>
<td>90 (95.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRA (No.)</td>
<td>82 (73.9)</td>
<td>53 (56.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter angiography (No.)</td>
<td>24 (21.6)</td>
<td>35 (37.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTA (No.)</td>
<td>2 (1.8)</td>
<td>2 (2.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Three deaths in the CA group, 4 deaths in the SAC group. For 1 patient in the SAC group (who died 298 days after treatment), the 1-year imaging was adjudicated using the 3-month follow-up angiogram.
Results for the secondary outcomes in the intent-to-treat analyses are detailed in Table 3. Secondary outcomes (immediate and 12 month angiographic outcomes, days of hospitalization, discharge disposition, mRS at discharge and at 12 months) were similar between groups. Angiographic results at 12 months were similar (RR 1.1; 95% CI 0.66 – 1.71; \( P = .789 \)). Changing the definition of a good angiographic outcome as a complete occlusion did not change results (Online supplemental data).

As-treated analyses included 198/205 patients (97%; seven patients treated with flow diverters were excluded). The primary outcome (treatment failure) occurred in 27/102 patients treated with SAC (26.5%; 95% CI, 18.4%–36.3%) compared with 29/94 (30.8%; 95% CI, 21.9%–41.3%) treated with CA (RR = 0.86; 95% CI, 0.55–1.34; \( P = .498 \)). Details of each component of the primary outcome are provided in Table 5.

Predefined as-treated subgroup analyses of the primary outcome are detailed and illustrated in the forest plot (Online Supplemental Data). There were no significant interactions, and subgroup results were similar.

In as-treated analyses, all-cause death or dependency at 1 year occurred in 10 of 104 (9.6%) SAC patients and in 4 of 94 CA patients (4.3%) (RR = 2.26; 95% CI, 0.73–9.96; \( P = .156 \)) (Table 6). Other secondary outcomes (Online Supplemental Data) (immediate angiographic outcomes, days of hospitalization, discharge disposition, and mRS at discharge and at 12 months) were similar between groups.

As-treated angiographic results at 12 months, categorized as the presence of a residual aneurysm or not, were not significantly different (RR = 0.77; 95% CI, 0.48–1.2; \( P = .300 \)). SAC was significantly better than CA in as-treated analyses when “complete occlusion” was used as the definition of a good angiographic outcome (RR = 0.74; 95% CI, 0.59–0.94; \( P = .012 \)) (Online Supplemental Data).

Adverse events (any severity) occurred in 34/104 (32.7%) patients who underwent SAC, compared with 12/94 (12.8%) patients with CA (RR = 2.56; 95% CI, 1.41–4.65; \( P = .002 \)). Details are provided in the Online Supplemental Data. Ischemic and hemorrhagic events were more frequent in patients who underwent SAC (30/104 [28.8%]) compared with 7/94 (7.4%) patients who received CA (RR = 3.87; 95% CI, 1.79–8.40; \( P = .001 \)).

---

**Table 4: Clinical outcomes (mRS > 2 at 12 months) in intent-to-treat analysis**

<table>
<thead>
<tr>
<th>Intent to treat</th>
<th>CA (n = 111)</th>
<th>SAC (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (No.) (%)</td>
<td>3 (2.7)</td>
<td>5 (5.3%)</td>
</tr>
<tr>
<td>Related</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Unrelated</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>mRS 3–5 (No.) (%)</td>
<td>3 (2.7)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Total (No.) (%)</td>
<td>6 (5.4)</td>
<td>8 (8.5)</td>
</tr>
</tbody>
</table>
patients.27,28 In ruptured aneurysms, they have been associated with a persistent risk of subarachnoid hemorrhage.27-29 In UIAs, they are more likely to occur in large, wide-neck, and recurrent aneurysms.23 In the context of a preventive treatment against ruptures, recurrences lead to a number of clinical consequences, such as routine angiographic surveillance of nearly all patients and retreatment in 5%-15%29 (even up to 25% of patients at 10 years in some series).30 In STAT, a substantial number of crossovers diluted the contrast between treatments. The classic way of analyzing results (intent to treat) remains clinically appropriate for practical reasons. First, many crossovers, such as bailout stent placement in patients with coil protrusion and parent vessel or branch occlusion (in the CA group) or failure to catheterize the branch necessary to land the stent (in the SAC group), were inevitable. Second, the goal of the trial was to assess the role of stent placement to intentionally improve the results of endovascular treatment. Perhaps the groups being compared could have been more precisely defined as SAC (if possible) versus CA plus bailout stent placement (only if necessary).

**DISCUSSION**

**The Problem of Residual Aneurysms after Coiling**

Residual or recurrent aneurysms after coiling occur in 10%-33% of patients.27,28 In ruptured aneurysms, they have been associated with a persistent risk of subarachnoid hemorrhage.27-29 In UIAs, they are more likely to occur in large, wide-neck, and recurrent aneurysms.23 Potentially more effective coils have been developed with varying potential to improve the angiographic results of coiling? Perhaps the groups being compared could have been more precisely defined as SAC (if possible) versus CA plus bailout stent placement (only if necessary).

**Stent Placement and Residual Aneurysms**

The use of SAC, originally designed to treat otherwise untreatable aneurysms, has expanded in the hope of decreasing the risk of recurrences.3,6-8,10-12,37-40 This hypothesis has never been tested in a randomized trial. Previous studies,3-12 including systematic reviews and meta-analyses,11,12 have shown diverging results. Some studies have reported that aneurysms treated with SAC were less prone to recurrence,3,5,8,10-12 while other studies did not show such an effect.4,6,7,9 Higher treatment-related risks of mortality and morbidity were shown in some reports,3,7,11 but not in others.4,6,8,10 Many studies reported significant baseline differences between the groups being compared, most often with characteristics that could favor SAC (ie, a high proportion of unruptured sidewall aneurysms and shorter follow-up time).3,5 Thus, after 20 years, we still lack reliable evidence regarding the risks and potential benefits of adding a stent to a coiling procedure in patients with UIAs eligible for both options. It is in this context of uncertainty that STAT was launched in 2011.

**The Choice of Primary Outcome**

The primary end point of STAT was a composite that included clinical and angiographic outcome measures. Although the main goal of UIA treatment is to prevent future ruptures, these are rare events.22-24 Using death or disability from rupture during follow-up would necessitate the recruitment of thousands of patients followed for a long time. Most clinicians rely on angiographic results to assess the efficacy of treatment, and most endovascular trials have used angiographic outcomes as primary end points.22-24 The residual aneurysm cutoff category was chosen to judge treatment failure because it has been shown to be more repeatable, and its clinical significance more constant than other categories.25 The clinical criteria included in the composite primary outcome measure ensured that a patient becoming dependent or dying because of a treatment-related complication (or because the treatment was clinically ineffective) would not count as a good outcome. However, clinical outcomes weighed little in the final comparison between treatments, which was driven mainly by angiographic results.

**Primary Outcome Results**

STAT did not show a large benefit of SAC over CA for the treatment of UIAs. This was true for patients with large (STAT-1), recurrent (STAT-2), or wide-neck aneurysms (STAT-3). The trial was only powered to show a large effect (a decrease in the failure rate from 33% to 15%). We cannot exclude that with the inclusion of a larger number of patients, a more modest but still clinically significant benefit could have been demonstrated.

In STAT, a substantial number of crossovers diluted the contrast between treatments. The classic way of analyzing results (intent to treat) remains clinically appropriate for practical reasons. First, many crossovers, such as bailout stent placement in patients with coil protrusion and parent vessel or branch occlusion (in the CA group) or failure to catheterize the branch necessary to land the stent (in the SAC group), were inevitable. Second, the goal of the trial was to assess the role of stent placement to intentionally improve the results of endovascular treatment. Perhaps the groups being compared could have been more precisely defined as SAC (if possible) versus CA plus bailout stent placement (only if necessary).

From an explanatory or mechanistic perspective, it is worth looking at the as-treated results: Does stent placement have the potential to improve the angiographic results of coiling?

Only by redefining a good angiographic outcome as a complete occlusion and only by looking at as-treated analyses could SAC be shown superior to CA (Online Supplemental Data). The clinical significance of this finding remains questionable, but it may be a signal in favor of the capacity of stent placement to improve angiographic results of coiling in the long term. This capacity may come at a cost in terms of complications: As-treated analyses also showed complications to be more frequent with SAC, particularly for small aneurysms. Although in some of these cases, complications occurred when stents were being used as a rescue strategy (ie, a technical complication had already occurred), thromboembolic complications with stent placement remain a concern.

**Safety of Treatments**

The overall morbidity and mortality of patients treated in STAT were within the range of our initial estimate (between 6% and 12%). Safety end points were similar between the 2 groups in intent-to-treat analyses, but the trial was underpowered to draw

### Table 5: Primary outcome in as-treated analysis

<table>
<thead>
<tr>
<th>As-treated analysis 1-year outcome</th>
<th>CA (n = 94)</th>
<th>SAC (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure (composite) (N) (%)</td>
<td>29 (30.9)</td>
<td>27 (26.0)</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 6</td>
<td>1 (1.1)</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>mRS 3–5</td>
<td>3 (3.2)</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retreatment</td>
<td>0</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td><strong>Angiographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate failure</td>
<td>3 (3.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Residual aneurysm (core lab)</td>
<td>22 (25.3)</td>
<td>16 (17.6)</td>
</tr>
<tr>
<td>Missing primary outcome</td>
<td>0</td>
<td>2 (1.9)</td>
</tr>
</tbody>
</table>

### Table 6: Clinical outcomes (mRS > 2 at 12 months) in as-treated analysis

<table>
<thead>
<tr>
<th>As-treated</th>
<th>CA (n = 94)</th>
<th>SAC (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (No.) (%)</td>
<td>1 (1.1)</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>Related</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Unrelated</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>mRS 3–5 (No.) (%)</td>
<td>3 (3.2)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Total (No.) (%)</td>
<td>4 (4.3)</td>
<td>10 (9.6)</td>
</tr>
</tbody>
</table>

*RR = 0.86; 95% CI, 0.55–1.34; P = .498.

**Table 5:** Primary outcome in as-treated analysis

**Table 6:** Clinical outcomes (mRS > 2 at 12 months) in as-treated analysis
any conclusions about the safety of SAC over CA. The upper limit of the 95% CI of the risk ratio of 4.4 cannot exclude SAC being associated with a large increase in initial or long-term neurologic deficits compared with CA. Cerebrovascular ischemic and hemorrhagic events in STAT were relatively high compared with previous registries and meta-analysis. However, those comparisons are not valid, and aneurysms randomized in STAT were typically larger and many were difficult to treat by any and all methods.

**Trial Limitations**

Before we examine the potential impact on clinical practice, we must review the trial limitations. Only 4 centers participated, which limits the generalizability of results. Although STAT is the only randomized controlled trial comparing SAC and CA, the number of patients remains small. The introduction of flow diverters likely directed many patients with difficult aneurysms to other clinical trials. The original plan was to recruit 40–50 centers, but the lack of financial support deterred many potential centers from participating. As many as 600 patients would have been necessary to exclude the possibility that SAC would double the risk of death or dependency. Yet, safety is of primary importance when a preventive treatment is offered to mostly asymptomatic individuals. Many advanced SAC techniques, such as X or Y stent placement, were not frequently used, and trial results cannot be applied to these treatments. Most stents were braided stents (83%), and results may not apply to other types of stents. There were a substantial number of crossovers, diluting the contrast between groups in the intent-to-treat analyses. The 12-month follow-up period was relatively short. This may not have given enough time for some recurrences to become apparent. Clinical outcome assessments were not blinded, and core laboratory adjudications could not be masked to the presence of artifacts caused by stents. Death or dependency accounted for a relatively small number of poor outcomes in both groups (5-versus-6 patients, including 2-versus-3 deaths). Thus, potential bias from lack of blinding of mRS clinical assessors is unlikely to have significantly affected results. There were some disparities in follow-up imaging modalities between groups. However, because only residual aneurysms, readily identified by any imaging technique, were considered in the adjudication of the primary outcome, this potential bias is unlikely to have affected the results. Finally, the trial was conducted during 10 years. Indications, devices, techniques, and clinical expertise have evolved over such a long period.

**Potential Implications for Practice and Future Research**

STAT results do not apply to patients excluded by protocol, such as those with ruptured aneurysms. They do not apply to most small UIAs because only patients at high risk for recurrence (with large, wide-neck, or recurrent aneurysms) were eligible. Patients judged untreatable without stent placement, a subjective notion, were also excluded by definition.

For patients with UIAs treatable by both options, the trial showed no large benefit of a policy of stent placement in addition to coiling. In addition, the trial raises concerns regarding potential thromboembolic complications. This was particularly true for patients with small aneurysms at low risk of rupture, for whom the crucial question remains: Should they be offered preventive treatment at all?

The use of stents for the treatment of UIAs is an example of the failure of our community to use randomized trials to safely introduce innovations in neurovascular care. We must find ways to integrate clinical research into practice to optimize care in real time. Future trials on SAC should probably be integrated into ongoing randomized clinical trials.

**CONCLUSIONS**

STAT did not show SAC to be superior to CA for wide-neck, large, or recurrent unruptured aneurysms. More randomized data are needed to determine the role of SAC in the treatment of aneurysms.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Radiology-Pathology and Surgical Correlation in Astroblastoma

F. Sprenger, E.B. da Silva Jr, M.S. Cavalcanti, and B.C. de Almeida Teixeira

ABSTRACT

SUMMARY: Astroblastoma is a rare astrocytic glial neoplasm that affects mainly young girls, peaking between 10 and 30 years of age, with low- and high-grade manifestations. Imaging characteristics are well-described, but histopathologic and, more recently, molecular analysis is fundamental to establish the diagnosis, now based on MN1 alterations. We describe a case with typical imaging and histologic features of an MN1-altered astroblastoma.

ABBREVIATIONS: 5-ALA = 5-aminolevulinic acid; AT/RT = atypical teratoid/rhabdoid tumor; GFAP = glial fibrillary acidic protein; Ktrans = volume transfer constant

A 9-year-old girl with a previous diagnosis of high-functioning autism spectrum disorder presented with a 2-day history of headache, vomiting, and sleepiness. On the first day of symptoms, she was seen at a pediatric emergency department and discharged with anesthesia. Due to progressive worsening and unresponsiveness to medication, she was referred to a neurologic tertiary facility. The clinical examination showed a preserved consciousness level and no focal neurologic deficits or signs of meningeal irritation. Blood work had no relevant findings. MR imaging was performed to rule out intracranial pathology.

**Imaging**

MR imaging showed a large, well-circumscribed intra-axial heterogeneous mass in the right frontal lobe (Fig 1). The lesion had an eccentric, solid component isointense to gray matter on T1 and T2, with intense heterogeneous enhancement due to multiple, small, nonenhancing cysts within the solid portion, giving the lesion a bubbly appearance.

Larger cystic areas were observed on the periphery of the lesion with an intermediate signal on FLAIR and hyperintensity on T2. Foci of hypointensity on SWI and hyperintensity on the filtered phase were also seen and interpreted as punctate calcifications.

A slight perilesional FLAIR hyperintensity was present and attributed to vasogenic edema. There was small mass effect, with a little, leftward, midline shift and right lateral ventricle compression.

Advanced sequences demonstrated foci of intensely restricted diffusion (ADC = $861 \times 10^{-6}$ mm$^2$/s), suggesting high cellularity, increased relative CBV (1.8×), and increased volume transfer constant ($K_{trans}$) (0.170). MR spectroscopy showed increased Cho/Cr and Cho/NAA ratios (6.98 and 2.26, respectively), suggesting cellular membrane breakdown with neuronal depletion and a prominent lipid-lactate peak, inferring necrosis (Fig 2).

The above-mentioned findings suggested an aggressive primary supratentorial neoplasm, like high-grade astrocytoma, ependymoma, and embryonal tumor, mainly atypical teratoid/rhabdoid tumor (AT/RT). Despite its rarity and nonspecific manifestations, overlapping with characteristics of the above-mentioned tumors, astroblastoma was also considered, given the patient’s age, the peripheral polymorph cysts, the solid enhancing portion with a bubbly appearance, and the well-circumscribed margins.

Neuraxis evaluation showed no additional lesions, and the patient underwent surgical resection 3 days after presentation at the tertiary center.

**Operative Report**

The patient was submitted to 5-aminolevulinic acid (5-ALA)-assisted microscopic near-total resection via frontal craniotomy. Perilesional thin-walled cysts were initially evacuated. The solid portion of the lesion was soft and heterogeneous, with an intense 5-ALA fluorescence and was resected with its capsule. The surgical cavity had faint 5-ALA positivity (Fig 3).

Intraoperative histopathologic examination showed a small-cell neoplasm with pseudorosettes, initially suggesting ependymoma.
Pathology: Astroblastoma

Grossly, the tumor was fragmented and was tan and soft, with an identifiable cystic membrane.

Histopathologic examination showed solid sheets and pseudopapillae of rhabdoid cells oriented radially toward vessels, forming astroblastic pseudorosettes (Fig 5). Findings also included necrosis and easily recognizable mitoses (up to 4 mitoses/10 high power fields).

Immunohistochemistry was positive for glial fibrillary acidic protein (GFAP) antibody, epithelial membrane agent, and D2-40 (podoplanin), with a Ki-67 index of 25%. Integrase interactor 1 (INI-1/SMARCB1) expression was retained. The final diagnosis was astroblastoma. MNI profiling was not possible due to limited availability.

Pathologic differential diagnosis is challenging, especially with ependymomas, because they also present with perivascular pseudorosettes. Astroblastic pseudorosettes, however, have distinct columnar, tapered, or cuboid cell borders oriented radially around a hyalinized vessel. On the other hand, ependymal pseudorosettes have unclear cell borders within a fibrillary perivascular area. Supratentorial ependymomas also tend to have infiltrative margins, not seen in our case, and RELA-fused tumors show L1CAM positivity on immunohistochemistry.

High-grade astrocytomas present as infiltrating astrocytic neoplasm with fibrillar glial processes, necrosis, and microvascular proliferation. Immunohistochemistry is positive for isocitrate dehydrogenase 1 (IDH1). These morphologic differences ruled out this diagnosis in our case.

Angiocentric glioma, gemistocytic astrocytomas, and glioblastomas can also present with focal areas of perivascular pseudorosettes and their infiltrative characteristics. Therefore, astroblastoma diagnosis should be reserved for well-circumscribed gliomas in which the gliovascular characteristic is the main finding.

AT/RT has variable patterns of histopathologic and immunostaining, consisting of rhabdoid cells, in addition to a small, blue, round cell component, and variable foci of mesenchymal or epithelial differentiation. Immunohistochemistry is usually positive for vimentin and epithelial membrane agent, and characteristically, have uncell cell borders within a fibrillary perivascular area.

FIG 1. MR images and tumor characterization on multiple sequences. A, Axial T2 image shows the right frontal solid-cystic mass, with large peripheral cysts (long arrow) and an eccentric bubbly-appearing solid component (short arrow). B, Axial FLAIR demonstrates that the signal intensity of the content of the peripheral cyst is not suppressed (asterisk), as well as mild perilesional edema (arrow). C, ADC map shows foci of intensely restricted diffusion on the anterior and solid aspect of the lesion (arrow). D, Axial SWI demonstrates foci of marked hypointensity (arrows), corresponding to punctate calcifications according to the filtered phase signal (not shown). E, Axial T1 image demonstrates an isointense to gray matter heterogeneous solid portion (short arrow) with a hypointense large peripheral cyst (long arrow). F, Axial T1 postgadolinium image shows intense heterogeneous enhancement of the solid part, with multiple small permeating cysts, giving the tumor a bubbly aspect (short arrow). The large peripheral cysts show no enhancement (long arrow).
there is a loss of either INI-1/SMARCBI or SMARCA4, the defining feature of this entity.4

**DISCUSSION**

Astroblastoma is a rare circumscribed astrocytic glial neoplasm, representing <3% of all gliomas, affecting mainly the cerebral hemispheres with a peak incidence between 10 and 30 years of age. Some series describe a higher prevalence in female patients.3,5,6 Its biologic behavior ranges from indolent to aggressive lesions, and a World Health Organization grade has not yet been attributed.1

Historically, astroblastomas were initially described by Bailey and Cushing in 1924,7 but their histopathologic and molecular features overlapping with diffuse astrocytomas, pleomorphic xanthoastrocytomas, and ependymomas have led to decades of confusion. It has been described as a stage of glioma dedifferentiation, a fiber-producing astrocytoma, or rare tanyocytes or ependymal astrocyte neoplasm. The term itself is confusing because they are not notoriously astrocytic nor blastic. Only recently, assisted by molecular advances, their reliable diagnostic criteria have been established.3,5,6 Recent genetic profiling of high-grade neuroepithelial tumors revealed that many of the lesions with recurrent *MN1* mutations had histologic features of astroblastoma.8

The *MN1* gene, located in chromosome 22, is involved in meningioma and myeloid leukemia pathogenesis, and its rearrangements can be detected through DNA methylation. In addition to astroblastoma, many central nervous system primary tumors may express *MN1* alterations, like circumscribed and diffuse gliomas. Recently, this molecular signature has been attributed to the latter for more accurate diagnosis, but further research is needed to establish the ways these rearrangements act in astroblastoma and how it differs from manifestations in similar neuroepithelial tumors.9-12

Therefore, astroblastoma still shows molecular heterogeneity, with no exclusivity of *MN1* mutations in all cases, with most being classifiable within the *MN1* or *BRAF* DNA methylation groups.9 Despite minor heterogeneity, *MN1* alterations have become the defining feature of this condition in the 2021 World Health Organization CNS tumor classification, which is now called *MN1*-altered astroblastoma.10

Imaging usually reveals a supratentorial peripherally located solid-cystic mass with little or no vasogenic edema and rarely adjacent parenchyma infiltration (Figure 4). A bubbly aspect is frequently seen due to multiple cysts. Calcifications are seen in most cases, more commonly in a punctate pattern within the solid part. The solid component is usually isointense on T1 and T2/
FLAIR, with a heterogeneous gadolinium enhancement and intermediate ADC values ranging from 1190 to 1250 \( \times 10^{-6} \) mm\(^2\)/s. Cystic areas are hyperintense on fluid-sensitive sequences and show facilitated diffusion. No MR imaging features can help differentiate indolent and malignant astroblastomas. Atypical presentations include solid masses with central necrosis and an irregularly rimmed cyst.3,6,13,14

Imaging differential diagnosis includes supratentorial ependymomas, astrocytomas, and AT/RT. YAP1 fusion-type ependymoma also presents as a heterogeneous mass with cystic areas. However, it is more prevalent among younger children, usually younger than 3 years of age. Due to its fibrillary components and infiltrative nature, perilesional edema and microinvasion are significantly more evident in ependymomas than in astroblastomas.5,6,13,14

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High-grade astrocytomas manifest less frequently in children but also have imaging features that overlap with astroblastoma because presentation may also demonstrate a heterogeneous supratentorial mass. Similar to ependymomas, mass effect and perilesional infiltration are more striking in astrocytomas compared with astroblastomas.16

AT/RT may also present as large supratentorial heterogeneous masses, with a peak incidence in younger children around 3 years of age. Imaging demonstrates solid-cystic masses, with frequent hemorrhage and intensely restricted diffusion, in contrast to astroblastoma. Leptomeningeal dissemination is also frequent in AT/RT but not expected in astroblastoma.4

Macroscopically, astroblastomas present as well-circumscribed solid-cystic masses with a bubbly appearance secondary to cystic degeneration. Microscopic features include elongated eosinophilic cells with GFAP-positive processes oriented radially from the cell body toward a usually hyalinized vessel, resembling ependymal perivascular pseudorosettes, but with a tapering or columnar aspect. Immunohistochemistry shows positivity for epithelial membrane agent and D2-40. GFAP, OLIG2, and S-100 are often positive to variable extents (Fig 5).3

Histologic features that indicate an aggressive biologic behavior include increased mitotic activity, palisading necrosis, high cellularity, vascular proliferation, and a high Ki-67 index. Higher Ki-67 indexes are also related to prognosis and survival rates, with a cutoff of 4%.1

A primary histopathologic differential diagnosis includes high-grade astrocytomas, supratentorial ependymomas, atypical teratoid/rhabdoid tumors, and gemistocytic astrocytoma and these are better discussed in the previous session (See Pathology: Astroblastoma).

Treatment relies on gross surgical resection whenever possible. Low-grade lesions with satisfactory excision are usually followed up. Patients with incomplete resection or high-grade features in histology usually undergo adjuvant radiation and systemic chemotherapy with temozolomide.12,17

Our patient had an excellent postoperative evolution, and 6-month control imaging shows no signs of recurrence. However, the multidisciplinary team opted for isolated adjuvant surgical cavity radiation due to faint 5-ALA surgical cavity positivity, necrosis, and mitotic activity. Systemic chemotherapy was not initiated.

Due to its rarity and imprecise imaging and histopathologic features, misdiagnosis is frequent. The ensemble of nonspecific features is the key. Astroblastoma should be remembered when this set of features is present, especially in a young female patient with a large, well-circumscribed hemispheric solid-cystic lesion.

**Case Summary**

- Astroblastoma is a rare intra-axial and hemispheric neoplasm typically present in adolescents and young adults.
- Imaging findings are not specific and include a heterogeneous mass with peripheral cysts and a solid bubbly-appearing component, overlapping with other tumors that affect children and young patients.

**FIG 3.** Intraoperative surgical microscope images. A, External view of the tumor demonstrates its peripheral cystic areas (arrow). B, Solid portion of the lesion after the cyst evacuation (arrow). C, The solid aspect of the tumor under blue light demonstrates its intense 5-ALA fluorescence (arrow).

**FIG 4.** The schematic representation of astroblastoma consists of a hemispheric heterogeneous lesion with a lobulated solid and eccentric component and peripheral larger cysts. Note the faint perilesional edema, disproportional to the size of the lesion.

FLAIR, with a heterogeneous gadolinium enhancement and intermediate ADC values ranging from 1190 to 1250 \( \times 10^{-6} \) mm\(^2\)/s. Cystic areas are hyperintense on fluid-sensitive sequences and show facilitated diffusion. No MR imaging features can help differentiate indolent and malignant astroblastomas. Atypical presentations include solid masses with central necrosis and an irregularly rimmed cyst.5,6,13,14

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**Case Summary**

- Astroblastoma is a rare intra-axial and hemispheric neoplasm typically present in adolescents and young adults.
- Imaging findings are not specific and include a heterogeneous mass with peripheral cysts and a solid bubbly-appearing component, overlapping with other tumors that affect children and young patients.
Pathologic differentiation from ependymoma can be challenging because both show perivascular rosettes. Subtle morphologic features can help differentiate astroblastic from ependymal pseudorosettes.

Recently, MN1 gene alterations have come to define this condition, which is now entitled MN1-altered astroblastoma.

The main imaging differential diagnoses include high-grade astrocytomas, AT/RT tumors, and supratentorial ependymoma.

Prognosis varies according to the presence of high-grade histologic findings, which also dictate adjuvant therapy.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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MR Imaging Signs of Gadolinium Retention Are Not Associated with Long-Term Motor and Cognitive Outcomes in Multiple Sclerosis


ABSTRACT

BACKGROUND AND PURPOSE: The long-term impact of gadolinium retention in the dentate nuclei of patients undergoing administration of seriate gadolinium-based contrast agents is still widely unexplored. The aim of this study was to evaluate the impact of gadolinium retention on motor and cognitive disability in patients with MS during long-term follow-up.

MATERIALS AND METHODS: In this retrospective study, clinical data were obtained from patients with MS followed in a center from 2013 to 2022 at different time points. These included the Expanded Disability Status Scale score to evaluate motor impairment and the Brief International Cognitive Assessment for MS battery to investigate cognitive performances and their respective changes with time. The association with qualitative and quantitative MR imaging signs of gadolinium retention (namely, the presence of dentate nuclei T1-weighted hyperintensity and changes in longitudinal relaxation R1 maps, respectively) was probed using different General Linear Models and regression analyses.

RESULTS: No significant differences in motor or cognitive symptoms emerged between patients showing dentate nuclei hyperintensity and those without visible changes on T1WIs ($P = .14$ and $0.92$, respectively). When we tested possible relationships between quantitative dentate nuclei R1 values and both motor and cognitive symptoms, separately, the regression models including demographic, clinical, and MR imaging features explained $40.5\%$ and $16.5\%$ of the variance, respectively, without any significant effect of dentate nuclei R1 values ($P = .21$ and $0.30$, respectively).

CONCLUSIONS: Our findings suggest that gadolinium retention in the brains of patients with MS is not associated with long-term motor or cognitive outcomes.

ABBREVIATIONS: BICAMS = Brief International Cognitive Assessment for MS; BVMT = Brief Visuospatial Memory Test; CVLT California Verbal Learning Test; DD = disease duration; DN = dentate nuclei; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GBCA = gadolinium-based contrast agent; Gd = gadolinium; GLM = General Linear Model; GMV = gray matter volume; SDMT = Symbol Digit Modalities Test; qMRI = quantitative MRI

The role of gadolinium-based contrast agents (GBCAs) in neuroradiologic clinical practice is unquestionable. Nevertheless, during the past years, possible consequences of their repeat administration have been reported. Since 2014, an increased interest in brain gadolinium (Gd) retention has emerged, especially for those patients undergoing multiple GBCA administrations during their life. This scenario applies to patients with malignancies as well as inflammatory conditions such as MS for whom contrast administration is recommended at the time of diagnosis and often repeated during clinical relapses and to monitor the effectiveness of disease-modifying therapy (DMT) and subclinical disease activity (particularly when previous studies for comparison are not available) or when opportunistic CNS infections are suspected.

From a radiologic standpoint, brain Gd retention results in the development of a T1WI hyperintensity detectable on conventional imaging at the level of deep gray matter structures, with particular reference to the globus pallidus and, mostly, the dentate nuclei (DN). Several ex vivo and preclinical models have confirmed this finding, linking the development of such modifications to the number of previous GBCA administrations and, in particular, to linear compounds, to the point that the use of some Gd chelates has been restricted since 2017.

However, while a large body of evidence supports the relationship between GBCA administration and development of
T1WI hyperintensity, the clinical impact of Gd deposition is still underexplored, and available investigations provide conflicting results. Indeed, no significant association has emerged between cumulative Gd exposure and the development of parkinsonism in a population study. In MS, while there seems to be no association between DN hyperintensity and worsening of motor symptoms, Gd retention has been associated with cerebellar dysarthria and lower verbal fluency scores. So far, to the best of our knowledge, only 1 study has explored long-term clinical outcomes of Gd deposition in a small cohort of patients with MS evaluated at different time points during follow-up.

Given this background, the aim of this study was to expand the current knowledge about the possible clinical impact of Gd accumulation in the brain, using MS as a model of a chronic condition with multiple exposures to GBCA. To accomplish this aim and investigate the presence of a delayed GBCA toxicity in patients with MS, we evaluated the long-term effects of GBCA retention on motor worsening, cognitive performance, and cognitive worsening during a 7-year follow-up period.

MATERIALS AND METHODS

Compliance with Ethical Standards

This study was approved by the local ethics committee (Carlo Romano Ethical Committee of the University of Naples “Federico II”, Approval no. 209/13) in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from each patient before enrollment.

Participants

This retrospective analysis was conducted on the same group of 74 patients with relapsing-remitting MS described in a previous work. Inclusion and exclusion criteria, as well as information about the number and type of previous GBCA administrations, were also reported in previously published works. All MR images used in the current analysis were acquired between 2013 and 2015. Given that these MR images were obtained before 2017, when the use of linear GBCA was limited by international agencies such as the European Medicines Agency, in some of these patients, a linear GBCA was administered (with a proportion of around 26% of linear GBCA, 45/175). Overall, a mean number of 6 GBCAs (range, 1–15) had been administered before the index MR imaging analyzed in the current work, all with the recommended standard doses. Of 74 patients, 32 (43.2%) had concomitant comorbidities (cardiovascular comorbidities, n = 11; autoimmune comorbidities, n = 11; psychiatric comorbidities, n = 7; digestive system comorbidities, n = 6; neurologic comorbidities, n = 5; metabolic comorbidities, n = 3; respiratory comorbidities, n = 3; genitourinary comorbidities, n = 1; musculoskeletal comorbidities, n = 1).

In line with expert consensus opinions and international guidelines on the use of MR imaging for disease monitoring, all patients underwent a yearly brain MR imaging with Gd from the time of diagnosis onward until the recent change in monitoring recommendations.

With reference to motor evaluation, 11 patients were lost to follow-up, leading to a final cohort of 63 subjects. All patients fulfilled the 2010 revision of the McDonald criteria at the time of MS diagnosis. The Expanded Disability Status Scale (EDSS) scores were obtained by experienced neurologists (V.B.M. and R.L, both with >25 years of experience) within 1 week from the baseline MR imaging and after a mean follow-up of 7.6 (SD, 0.6) years. Changes in the EDSS score (ΔEDSS) were calculated, in line with a previous study, as the subtraction of EDSS score on follow-up from the baseline EDSS score, defining motor worsening if a subject showed a ΔEDSS of ≥ 1 (for a baseline EDSS ≤ 5.5) or ≥0.5 (for a baseline EDSS > 5.5).

Although cognitive evaluations were not routinely performed at the time of the baseline MR imaging and from 2020 to 2022 due to practice modifications related to the pandemic, the Brief International Cognitive Assessment for MS (BICAMS) battery was collected for most enrolled subjects (65/74, 87.8%) by an experienced neuropsychologist (F.F., with >10 years of experience) after a mean follow-up of 4.6 (SD, 1.0) years and in a subset of 32 patients also after 7.5 (SD, 0.7) years from baseline MR imaging.

Briefly, the BICAMS includes the Symbol Digit Modalities Test (SDMT) to assess attention and processing speed, the California Verbal Learning Test (CVLT) to assess episodic verbal learning and memory, and the Brief Visuospatial Memory Test (BVMT) to assess visuospatial memory. Corresponding z scores were estimated according to previous works. Patients were defined as cognitively impaired if they showed at least 1 of the z score values of equal or less than −1.5. For the ancillary analysis, cognitive worsening with time was defined by a zBICAMS of equal or less than −0.5, calculated as a subtraction of the mean zBICAMS at 7.5 years from the mean zBICAMS at 4.6 years.

Finally, the number of new relapses and disease duration (DD) were collected as additional clinical variables.

MR Imaging Data Acquisition and Analysis

A complete description of MR imaging data acquisition and analysis is available in a previous work. Briefly, MR imaging signs of Gd retention were qualitatively evaluated on unenhanced T1WIs, recording the presence of a visible bilateral hyperintensity affecting both DN (Fig 1). A quantitative MR imaging (qMRI) analysis of GBCA accumulation was achieved through the calculation of qMRI maps according to previous works and automatically extracting mean R1 values after the placement of 2 irregular bilateral ROIs on the axial section with the best representation of the DN (Fig 2).

Finally, hyperintense lesions were detected and segmented on FLAIR images with a semiautomated approach (Jim7; Xinapse Systems) to obtain lesion load volumes and for the inpainting procedure. By means of FSL SIENAX (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA), the T1WI volumes were processed to extract gray matter volume (GMV), normalized for the corresponding V-scaling factor, as a measure of cortical atrophy.

Statistical Analysis

To evaluate possible differences in terms of age and DD between stable and motor or cognitively worsened patients, we performed
an independent 2-samples t test, while differences in terms of sex were tested through a \( \chi^2 \) test.

Possible differences in terms of \( \Delta \text{EDSS} \) between patients with and without DN hyperintensity, along with possible differences of DN R1 values between stable and motor-worsened patients, were probed via the General Linear Model, accounting for potential confounding factors (age, sex, MS phenotype, DMT, GMV, lesion load, DD, and new relapses). Furthermore, the possible relationship between \( \Delta \text{EDSS} \) and DN R1 values was tested via hierarchical multiple linear regression analysis, including clinical and demographic variables (sex, age, MS phenotype, DMT, DD, and new relapses) in the first block and MR imaging variables in the second one. For the cognitive evaluation, possible differences in terms of \( z \) scores of each BICAMS battery test between patients with and without DN hyperintensity, along with possible differences of DN R1 values between stable and cognitively worsened subjects, were tested using a GLM similar to the one previously described for the motor analyses. A similar hierarchical multiple linear regression analysis was also performed to test the possible relationship between BICAMS test \( z \) scores and clinical, demographic, and MR imaging variables.

Finally, the same analyses were also performed to compare \( \Delta \text{BICAMS} \) between patients with and without DN hyperintensity and probe the possible relationship between DN R1 and the development of cognitive worsening or between \( \Delta \text{BICAMS} \) and DN R1 values.

Methods and subsequent results of an additional subanalysis evaluating possible differences in terms of DN R1 values among subjects undergoing DMT changes with time are reported in the Online Supplemental Data.

**RESULTS**

A complete list of demographic and clinical information of the studied population for motor and cognitive data is available in Tables 1 and 2, respectively.

At baseline, 73/74 patients (98.7%) were in treatment with a DMT: fingolimod, \( n = 17 \); natalizumab, \( n = 28 \); interferon \( \beta \)-1a, \( n = 20 \); interferon \( \beta \)-1b, \( n = 7 \); and glatiramer acetate, \( n = 1 \). During a follow-up period of \( >7 \) years, 27.0% (17/63) of patients did not undergo therapeutic switches, whereas the remaining patients switched therapy once (55.5%, 35/63) or more (17.5%, 11/63) than once (natalizumab, \( n = 20 \); fingolimod, \( n = 14 \); cladribine, \( n = 7 \); interferon \( \beta \)-1b, \( n = 7 \); glatiramer acetate, \( n = 1 \)).

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**Table 1: Demographic and motor clinical variables of the subjects included in this study**

<table>
<thead>
<tr>
<th>Motor Examination</th>
<th>Baseline ( n = 74 )</th>
<th>Follow-Up ( n = 63 )</th>
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<tr>
<td>Age (mean) (range) (yr)</td>
<td>36.1 (SD, 10.1) (21–62)</td>
<td>44.4 (SD, 10.4) (28–69)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>27:47</td>
<td>26:37</td>
</tr>
<tr>
<td>DD (mean) (yr)</td>
<td>9.8 (SD, 6.8)</td>
<td>18.3 (SD, 7.0)</td>
</tr>
<tr>
<td>EDSS (median) (range)</td>
<td>3.0 (1.5–6.5)</td>
<td>2.5 (1.0–7.5)</td>
</tr>
<tr>
<td>Follow-up time from baseline (mean) (yr)</td>
<td>NA</td>
<td>7.6 (SD, 0.6)</td>
</tr>
<tr>
<td>( \Delta \text{EDSS} ) (mean)</td>
<td>NA</td>
<td>-0.3 (SD, 0.9)</td>
</tr>
<tr>
<td>Clinical progression (progressed/stable)</td>
<td>NA</td>
<td>6/57</td>
</tr>
</tbody>
</table>

**Note:** NA indicates not applicable.

*Motor worsening was defined if a subject showed a \( \Delta \text{EDSS} \equiv 1 \) (for baseline EDSS \( \leq 5.5 \)) or \( \equiv 0.5 \) (for baseline EDSS \( > 5.5 \)).

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With reference to motor performances, 6 of 63 patients (9.5%) showed a motor worsening at follow-up, with 4 of these patients converting to a secondary-progressive course. Stable and worsened patients did not differ in terms of age ($P = .39$) or sex ($P = .91$), while a significant difference in EDSS ($P = .04$) emerged. When we compared subjects showing DN hyperintensity at baseline with patients without any detectable change on unenhanced T1WI, no significant difference emerged in terms of AEDSS ($P = .14$) (Fig 3A). Similarly, no significant difference was found in terms of DN R1 between stable subjects and patients showing motor worsening ($P = .15$) (Fig 3B).

When we tested for a possible relation between DN R1 values and AEDSS, the regression model with clinical and demographic variables explained only 24.0% of the variance of AEDSS, whereas adding to the model lesion load and GMV increased the explained variance by 16.5% (40.5%, $P = .005$). When we evaluated independent predictors, the only significant effect was identified for GMV ($P = .04$), without any significant effect of DN R1 values in explaining the AEDSS variance ($P = .21$) (Fig 4A).

With reference to cognitive performances, 40 of 65 patients (61.5%) presented with cognitive impairment at a mean of 4.6 years of follow-up. These subjects did not differ from cognitively preserved patients in terms of age ($P = .87$), sex ($P = .44$), and EDSS ($P = .37$). Similarly, no significant differences were observed between patients with and without DN hyperintensity on MR imaging in terms of BICAMS $z$ score ($P = .92$) or its individual components ($P = .96$ for the SDMT; $P = .41$ for the BVMT; $P = .53$ for the CVLT) (Fig 5A). Finally, the group of patients with cognitive impairment was not different in terms of mean DN R1 values ($P = .26$) compared with cognitively preserved subjects (Fig 5B).

When we investigated the relation between DN R1 values and BICAMS scores, the model explained 16.5% of the variance, without a significant effect of DN R1 in explaining BICAMS $z$ scores ($P = .30$) or its components ($P = .40$ for the SDMT; $P = .24$ for the BVMT; $P = .61$ for the CVLT).

Finally, in the subset of patients with follow-up examinations available at 7.5 years, 5 of 32 patients (15.6%) showed cognitive worsening. These subjects were not different in terms of age ($P = .96$), sex ($P = .60$), DD ($P = .19$), or R1 values ($P = .18$) compared with stable patients. Similarly, there were no significant differences in terms of $\Delta$BICAMS between patients with and without DN hyperintensity on MR imaging ($P = .27$) and no significant effect of DN R1 values in explaining the $\Delta$BICAMS variance ($P = .28$) (Fig 4B).

Table 2: Demographic and cognitive clinical variables of the subjects included in this study

<table>
<thead>
<tr>
<th>Cognitive Examination</th>
<th>First Follow-Up ($n = 65$)</th>
<th>Second Follow-Up ($n = 32$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean) (range) (yr)</td>
<td>36.5 (SD, 10.1) [21–62]</td>
<td>45.9 (SD, 10.5) [29–61]</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>26–39</td>
<td>13–39</td>
</tr>
<tr>
<td>DD (mean) (yr)</td>
<td>15.0 (SD, 7.1)</td>
<td>18.6 (SD, 7.7)</td>
</tr>
<tr>
<td>SDMT $z$ score (mean)</td>
<td>–1.3 (SD, 1.2)</td>
<td>–1.1 (SD, 1.3)</td>
</tr>
<tr>
<td>BVMT $z$ score (mean)</td>
<td>–0.9 (SD, 1.5)</td>
<td>–0.6 (SD, 1.4)</td>
</tr>
<tr>
<td>CVLT $z$ score (mean)</td>
<td>–0.6 (SD, 1.4)</td>
<td>–0.4 (SD, 1.5)</td>
</tr>
<tr>
<td>BICAMS $z$ score (mean)</td>
<td>–0.9 (SD, 1.1)</td>
<td>–0.7 (SD, 1.0)</td>
</tr>
<tr>
<td>FU time from baseline (mean) (yr)</td>
<td>4.6 (SD, 1.0)</td>
<td>7.5 (SD, 0.7)</td>
</tr>
<tr>
<td>$\Delta$BICAMS (mean)</td>
<td>NA</td>
<td>–0.3 (SD, 0.8)</td>
</tr>
<tr>
<td>Cognitive impairment (impaired/preserved)</td>
<td>40/25</td>
<td>NA</td>
</tr>
<tr>
<td>Cognitive progression</td>
<td>NA</td>
<td>3/32 (15.6%)</td>
</tr>
</tbody>
</table>

Note: – FU indicates follow-up.

*Cognitive impairment at the first time point was defined if a subject showed at least one of the $z$ score values of equal or less than –1.5. Cognitive worsening at second time point was defined in case of $\Delta$BICAMS equal or less than –0.5.

FIG 3. Boxplots showing $\Delta$EDSS (A) and DN R1 values (B) of patients with and without a DN hyperintensity on unenhanced T1WI and motor worsening, respectively. Motor worsening was defined if a subject showed a $\Delta$EDSS $\geq 1$ (for baseline EDSS $\leq 5.5$) or $\geq 0.5$ (for baseline EDSS $> 5.5$). R1 values are expressed as $s^{-1}$. 

DISCUSSION

A significant body of literature regarding Gd accumulation in tissues of patients with normal renal function has been published.\textsuperscript{2,3,6,9} Given that brain Gd retention occurs mainly in the DN,\textsuperscript{2,3,6,9} we investigated whether qualitative and quantitative MR imaging signs of Gd accumulation in this region would correlate with clinical changes with time.

With reference to motor performance, we found no significant difference in terms of DN R1 between stable and motor-worsened patients, in line with previous studies showing no significant association between GBCA exposure and the development of parkinsonism.\textsuperscript{10} Similarly, a case series in patients with glioblastoma multiforme\textsuperscript{24} who received at least 50 GBCA injections during 10 years did not identify any clinical impairment possibly related to Gd deposition. Additionally, our results expand findings from previous cross-sectional and short-term longitudinal studies in MS, reporting no association between motor disability and DN Gd deposition.\textsuperscript{11,25,26} Overall, these results are in line with the hypothesis of an absence of direct damage affecting the DN due to Gd deposition, given that this structure plays a key role in the physiology of the motor control loop\textsuperscript{27} and its involvement should, therefore, result in the development of harmful and disruptive motor symptoms similar to those observed in animal models in which direct damage to this structure has been induced.\textsuperscript{28}

Exploring the cognitive counterpart of Gd retention, we did not find a significant association between cognitive impairment and mean DN R1 values, also in line with findings in most of the available literature.\textsuperscript{29,30} However, 2 studies in patients with MS\textsuperscript{12,25} previously reported a possible association between Gd retention and lower verbal fluency performance. One study\textsuperscript{12} observed an association between high signal DN intensity and low verbal fluency performances, and it might be tempting to quickly settle this matter by indicating, in the obvious advantages of qMRI, the most plausible explanation for these differences. Indeed, the same authors\textsuperscript{25} failed to confirm this association when evaluating quantitative R1 values. Nevertheless, in this same latter study, a mild correlation between poor information-processing speed (as measured by the SDMT)
and DN R1 values was identified. Here, after analyzing a group of patients with MS with similar demographic and clinical features and a similar quantitative approach, we were not able to confirm this finding. These discrepancies across studies might be explained by several factors, and we fully agree that MS pathology might be confounding the results. Here, to address this issue and although we acknowledge that overcorrection might be a possible pitfall in statistical analysis, we have considered many known confounders that might account for changes in the SDMT results and failed to find any significant associations between SDMT and DN R1 values.

This result, corroborated by the absence of other significant associations within the cognitive domains assessed by the BICAMS, strengthens the hypothesis of an absence of a significant clinical impact of Gd retention in the brain, in line with recent preclinical observations showing no behavioral alterations in mice that developed T1WI hyperintensity on MR imaging after multiple injections of linear GBCA. Although the role of the cerebellum in language is well-recognized, verbal fluency tasks seem to be more related to the lateral portion of the hemispheres rather than the DN itself, as also confirmed by a coordinate-based activation likelihood estimation meta-analysis on brain activation during both phonemic and semantic verbal fluency tasks. Furthermore, given the above-mentioned role of the DN as a main relay of several different motor and cognitive loops, it seems very unlikely that among all the functions that might have been affected by Gd retention, only verbal fluency, which is characterized by a complex interplay of a variety of cognitive functions and brain areas, could have been involved. Similar considerations also apply to the correlation between increased DN T1WI hyperintensity and mild dysarthria observed in a different study, because dysarthria is usually related to hemispheric damage, with a preponderant right lateralization.

Finally, we acknowledge that different from the motor analysis in which GMV proved to be an independent predictor of disability, we did not identify any MR imaging predictor of cognitive impairment. A possible explanation of this result should be researched in a more profound and prominent involvement of other brain areas, such as the deep gray matter, in explaining the development of cognitive deficits in MS.

This study has some limitations. As previously discussed, due to its retrospective nature, we were not able to investigate some features, such as dysarthria or verbal fluency, which could have been of interest; a direct investigation of the correlation between qMRI changes affecting the DN and verbal fluency or dysarthria is, therefore, warranted. Another limitation is the relatively low number of patients investigated, which might have limited the sensitivity toward smaller effect sizes as well as preventing us from performing a subgroup analysis comparing linear and macrocyclic GBCAs. Nevertheless, this represents a trade-off for the use of qMRI evaluation, that in change provides more accurate evaluation of Gd retention compared with qualitative conventional MR imaging.

CONCLUSIONS
Although characterized by these limitations, our results suggest that Gd accumulation, indirectly assessed via qualitative and qMRI parameters, is not associated with detectable clinical correlates in terms of global motor and cognitive worsening in MS.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES
Clinical Profiles and Patterns of Neurodegeneration in Amyotrophic Lateral Sclerosis: A Cluster-Based Approach Based on MR Imaging Metrics


ABSTRACT

BACKGROUND AND PURPOSE: The previous studies described phenotype-associated imaging findings in amyotrophic lateral sclerosis (ALS) with a prior categorization of patients based on clinical characteristics. We investigated the natural segregation of patients through a radiologic cluster-based approach without a priori patient categorization using 3 well-known prognostic MR imaging biomarkers in ALS, namely bilateral precentral and paracentral gyrus cortical thickness and medulla oblongata volume. We aimed to identify clinical/prognostic features that are cluster-associated.

MATERIALS AND METHODS: Bilateral precentral and paracentral gyri and medulla oblongata volume were calculated using FreeSurfer in 90 patients with amyotrophic lateral sclerosis and 25 healthy controls. A 2-step cluster analysis was performed using precentral and paracentral gyri (averaged pair-wise) and medulla oblongata volume.

RESULTS: We identified 3 radiologic clusters: 28 (31%) patients belonged to “cluster-1”; 51 (57%), to “cluster 2”; and 11 (12%), to “cluster 3.” Patients in cluster 1 showed statistically significant cortical thinning of the analyzed cortical areas and lower medulla oblongata volume compared with subjects in cluster 2 and cluster 3, respectively. Patients in cluster 3 exhibited significant cortical thinning of both paracentral and precentral gyri versus those in cluster 2, and this latter cluster showed lower medulla oblongata volume than cluster 3. Patients in cluster 1 were characterized by older age, higher female prevalence, greater disease severity, higher progression rate, and lower survival compared with patients in clusters 2 and 3.

CONCLUSIONS: Patients with amyotrophic lateral sclerosis spontaneously segregate according to age and sex-specific patterns of neurodegeneration. Some patients with amyotrophic lateral sclerosis showed an early higher impairment of cortical motor neurons with relative sparing of bulbar motor neurons (cluster 3), while others expressed an opposite pattern (cluster 2). Moreover, 31% of patients showed an early simultaneous impairment of cortical and bulbar motor neurons (cluster 1), and they were characterized by higher disease severity and lower survival.

ABBREVIATIONS: ALS = amyotrophic lateral sclerosis; ALSFRS-r = ALS Functional Rating Scale-Revised; CS = control subjects; IQR = interquartile range; MOv = medulla oblongata volume; ODI = onset-to-diagnosis interval; ParaCT = paracentral gyrus; PreCT = precentral gyrus

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease known for its extremely heterogeneous natural course.1 Early identification of patients characterized by a faster disease progression rate is one of the primary goals in the field of motor neuron diseases to provide correct information about prognosis, care needs, and support services.

Several staging systems were previously proposed to stratify patients according to the phase of the disease and cognitive profiles and to identify prognostic factors.2-7 The feasibility of these staging systems has been proved in both trials and the clinical setting, by successfully allocating patients into specific disease categories. Several standard procedures have been proposed to guarantee interrater reliability in assessing the correct staging.8,9 However, until now, clinical staging still requires the careful consideration of observed clinical parameters and relies invariably on the interpretation of reported symptoms and other potentially subjective factors. Therefore, several quantitative biomarkers,10,11 beyond clinical parameters, have been proposed to correctly distinguish subgroups of patients according to different prognoses.

Among different “dry biomarkers,”12 MR imaging has progressively acquired greater relevance to assess in vivo the extent of CNS damage in patients with ALS, given its accessibility and non-invasiveness. A recent review stated that the most disease-sensitive...
MR imaging patterns are located in motor regions. Specifically, disease severity (expressed as ALS Functional Rating Scale-Revised [ALSFRS-r] score) and progression rate correlated with the mean cortical thickness of the motor area, extramotor areas (eg, paracentral lobules), and medulla oblongata volume (MOv). These MR imaging metrics have also been proposed as predictive biomarkers of survival.

Nonetheless, most imaging studies validated MR imaging metrics by describing phenotype-, genotype-, or stage-associated radiologic profiles in a priori selected clinical categorizations (eg, spinal or bulbar onset, fast and slow progressors, prevalent upper or lower motor neuron impairment). An alternative interesting approach was recently performed by Bede et al, which used cluster analysis of pooled imaging data and subsequent analysis of cluster-associated clinical characteristics. Using a large unsegregated MR imaging data set and 74 MR imaging metrics, the authors found that patients with ALS spontaneously segregated in 2 clusters mainly according to 3 specific areas, namely superior temporal and superior and inferior frontal gyri. The 2 clusters exhibited different frontotemporal impairment on MR imaging and the prevalence of C9orf72 mutation carriers. In line with this study, Tan et al found that patients with ALS could be divided into 3 subgroups (pure motor neuron; orbitofrontal and temporal involvement; posterior cingulate cortex, parietal white matter temporal operculum and cerebellum) using a connectome-based clustering algorithm among 68 cortical regions, 15 subcortical structures, and all the white matter tracts between these latter regions.

Different from these latter studies, we restricted our cluster-based analysis to MR imaging metrics identified as core features of disease severity and survival in ALS by previous reports, namely cortical thickness of the precentral gyrus (PreCT) and paracentral gyrus (ParaCT) and MOv. Thus, we aimed to identify the clinical and prognostic features of the different radiologic clusters.

**MATERIALS AND METHODS**

**Ethics Approval**

We confirm that we have read AJNR’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Ethics approval was waived by the local ethics committee, considering that all the procedures being performed were part of the routine care (study No. 6778).

**Population**

A total of 90 incident patients with ALS referred to our ALS tertiary center between 2018 and 2020 were consecutively recruited at the time of diagnosis. A careful diagnostic work-up was performed to exclude ALS-mimicking diseases. All patients met the criteria for clinically definite, probable, or possible ALS according to the El Escorial-revised criteria. Exclusion criteria included prior cerebrovascular events, traumatic brain injury, neurosurgical procedures, as well as neoplastic, paraneoplastic, or neuroinflammatory comorbidities.

None of the patients fulfilled the criteria for ALS and frontotemporal dementia according to the Strong criteria. Demographic characteristics and clinical data have been registered and collected by experienced neurologists of the ALS team. We recorded the following demographic and clinical variables: age at symptom onset, sex, onset-to-diagnosis interval (ODI), age at diagnosis (corresponding to the first neurologic clinical evaluation), site of symptom onset, and clinical phenotype.

All patients were functionally evaluated using the ALSFRS-r. The progression rate was calculated using the following formula: \((48 – \text{ALSFRS-r}) / \text{disease durations (months)}\).

Longitudinal clinical evaluations were performed at 4- to 6-month intervals, and data regarding death or tracheostomy were recorded. The censoring date was set at March 31, 2022. Tracheostomy or death (if it occurred) were considered as a composite outcome.

Control subjects (CS) consisted of 25 subjects, not affected by inflammatory, autoimmune, and vascular or neurodegenerative diseases, without a family history of ALS and without abnormal findings on brain MR imaging.

**MR Imaging Acquisitions**

All participants underwent MR imaging on a 1.5T MR imaging scanner (Philips) at Azienda Ospedaliero Universitaria Policlinico of Bari. Specifically, patients with ALS underwent MR imaging at the time of diagnosis, concurrent with their first neurologic evaluation. Routine T1-, T2-weighted, and FLAIR sequences were performed to exclude other causes of focal or diffuse brain damage, including lacunar and extensive cerebrovascular lesions. 3D structural MR imaging was acquired using a T1-weighted MPRAGE sequence (TR/TE/flip angle = 25.00 ms/4.60 ms/30.00°, FOV = 240 mm, matrix = 256 × 256, voxel size = 0.93 × 0.93 × 1.0 mm³).

**Cortical Thickness Analysis and Volumetric Analysis**

FreeSurfer software, Version 7.1 (http://surfer.nmr.mgh.harvard.edu) was used to assess cortical thickness. Processing steps included correction for magnetic field inhomogeneity, alignment to a specific atlas, skull removal, and segmentation of voxels into GM, WM, and CSF. Cortical thickness was then calculated on the basis of the shortest distance of 2 surfaces: the interface between GM and WM and the pial surface. The anatomic labels of the Desikan–Killiany atlas were used to calculate average cortical thickness in the precentral and paracentral cortical regions in the left and right temporal hemispheres separately.

MOv was obtained using the FreeSurfer tool “segmentBS25.” Segmentation (https://surfer.nmr.mgh.harvard.edu/segmentation/BrainstemSubstructures) was conducted using a robust and accurate Bayesian algorithm, relying on a probabilistic atlas of the brainstem and neighboring anatomic structures implemented in FreeSurfer. Additionally, from each preprocessed T1-weighted data set, total intracranial volume was calculated using FreeSurfer. Raw volumetric values of the medulla oblongata were corrected for the total intracranial volume using the residual method.

**Statistical Analysis**

The bilateral PreCT and ParaCT were averaged pair-wise and, together with MOv, were included in the 2-step cluster analysis. The choice of using the left and right precentral and paracentral cortical thicknesses averaged pair-wise is
consistent with previous studies that showed that cortical atrophy in these latter regions occurred early and bilaterally, especially in patients with ALS with bulbar-onset\textsuperscript{34} and, irrespective of the side of first limb weakness, in patients with ALS with spinal onset.\textsuperscript{35} Furthermore, because interhemispheric asymmetry was found in healthy subjects,\textsuperscript{36} the inclusion of MR imaging metrics belonging to both the right and left hemispheres could have biased the entire analysis by finding clusters that are subject-related and not disease-related. Therefore, we included the pair-wise average precentral and paracentral cortical thickness, to provide an overall measure of cortical atrophy, as performed elsewhere.\textsuperscript{32,36}

Both cortical thickness and volumetric measures were minimum-maximum normalized to a 0–1 scale, to account for different measurements scales. The 2-step cluster analysis was performed using the Euclidean distance measure. The number of clusters was not fixed a priori, and the Bayesian information criterion was used to determine the number of clusters. On the basis of cluster membership of individual patients, cluster sizes were determined and silhouette analyses were run using the STATS CLUS SIL extension of SPSS (IBM).\textsuperscript{26}

ANCOVA was performed to evaluate differences in MR imaging metrics between the following groups: first, between CS and each radiologic ALS cluster and then among patients with ALS belonging to different clusters. In the analysis, PreCT and ParaCT and MOv were included as dependent variables, and study groups as categoric independent variables. Age at the first neurologic evaluation (time of diagnosis) and sex were considered potential confounding factors,\textsuperscript{37} and they were used as covariates.

Demographic and clinical variables of the entire ALS population and of each cluster patient were reported as median (along with interquartile range [IQR]) or frequencies (percentages) for continuous and categoric variables, respectively. Group differences in the demographic and clinical variables were evaluated using a Mann-Whitney U test for continuous variables and the $\chi^2$ or Fisher exact test for categoric variables.

To evaluate the different prognoses of each cluster, we dichotomized all patients with ALS into long and short survivors using the 2-step cluster analysis.\textsuperscript{38} Categoric variables (reaching or not reaching the end point) and continuous variables (time elapsed between symptoms onset and censoring date or end points) were included in the model. Logistic regression was used to test the different percentages of short and long survivors in each cluster. The results were reported as OR and 95% CI. Last, Kaplan-Meier survival curves were used to illustrate the distribution of survival, and log-rank tests were used to test for differences among different radiologic clusters.

**RESULTS**

**Clinical and Demographic Characteristics of the ALS Population and CS**

The median age at symptom onset was 57 years, and the median ODI was 10 months. The spinal onset of disease was more frequent than bulbar onset (74% and 26%, respectively). Sixty-eight patients (76%) were classified as classic ALS phenotypes.\textsuperscript{1} Twenty-two (24%) patients were classified as having “definite ALS” according to the El Escorial-revised criteria.\textsuperscript{4} Sixty-five (72%) patients reached the composite outcome (tracheostomy or death) at the censoring date. The estimated median survival time from symptom onset to combined outcome was 47 months (Table).

CS were sex- and age-matched to patients with ALS with a median age of 54 years (IQR = 45–57 years) and a male-to-female ratio of 14:11 (56% male and 44% female).

**MR Imaging Metrics**

Two-step cluster analysis identified 3 distinct clusters of anatomic disease burden distribution: among all patients with ALS, 28 (31%) belonged to cluster 1; 51 (57%), to cluster 2; and 11, (12%) to cluster 3. The silhouette coefficient of 0.6 indicates reasonable cohesion and separation according to Kaufman and Rousseau.\textsuperscript{39}

In comparison with CS, patients with ALS in cluster 1 exhibited significantly lower values of both PreCT and ParaCT and MOv ($P < .001$ for all). Patients with ALS in cluster 2 had lower values of MOv compared with CS ($P < .001$), whereas patients with ALS in cluster 3 showed significantly lower PreCT and ParaCT values ($P = .001$), but no differences in MOv (Fig 1).

Patients with ALS in cluster 1 showed significantly lower PreCT and ParaCT values compared with those in cluster 2 ($P < .001$ for both), but not patients in cluster 3. Furthermore, the patients with ALS in cluster 1 had lower MOv values than those in cluster 3 ($P < .001$), but not patients in cluster 2. On the other hand, patients with ALS in cluster 2 exhibited significantly lower values of MOv ($P < .001$) compared with those in cluster 3, and in turn, this latter cluster had lower values of both PreCT and ParaCT than cluster 2 ($P = .001$ for both) (Fig 1).

**Clinical and Demographic Features of the 3 Clusters**

The Table shows the cluster-associated ALS clinical and demographic features.

The 3 clusters differed in age and sex: specifically, patients with ALS in cluster 1 were older than those in cluster 2 and cluster 3 ($P = .045$ and $P = .001$, respectively), while no differences were found between these latter 2 groups (Table). Male prevalence was 57% and 82% in clusters 2 and 3, respectively, while female prevalence was 68% in cluster 1 ($P = .035$ and $P = .005$, respectively).

No statistically significant differences were found in the ODI among the 3 groups. A spinal onset of the disease was found in all patients with ALS in cluster 3 and in about 70% of patients with ALS in both clusters 1 and 2. Patients with ALS in cluster 1 also had a higher diagnostic certainty, expressed by a higher percentage of “definite ALS” according to the El Escorial-revised criteria, compared with those in cluster 2 (43% versus 16%, $P < .001$) and cluster 3 (43% versus 18%, $P = .017$).

Patients with ALS in cluster 1 had an overall higher disease severity, expressed by lower ALSFRS-r scores than patients in both cluster 2 and cluster 3 ($P = .001$ and $P < .001$, respectively), while no differences were found between these latter 2 groups. Furthermore, patients with ALS in cluster 1 showed a higher progression rate compared with those in cluster 2 and cluster 3 ($P = .002$ and $P = .02$, respectively).

**Survival Analysis**

Among our study cohort, 26 patients were included in the long survivors’ group with a median time of observation of 57 months (IQR = 45–80 months), and none of them reached the composite
**Association between MR imaging clusters and clinical features in patients with ALS**

<table>
<thead>
<tr>
<th></th>
<th>ALS Population (n = 90)</th>
<th>Cluster 1 (n = 28)</th>
<th>Cluster 2 (n = 51)</th>
<th>Cluster 3 (n = 11)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (median) (IQR) [yr]</td>
<td>57 (50–65)</td>
<td>67 (62–70)</td>
<td>41 (44–54)</td>
<td>46 (45–54)</td>
<td>P = .045&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex (No. of patients) [male/female]</td>
<td>47:43</td>
<td>9:19</td>
<td>29:22</td>
<td>9:2</td>
<td>P = .001&lt;sup&gt;e&lt;/sup&gt;, P = ns&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Site of onset (spinal/bulbar) (No. of patients)</td>
<td>67/23</td>
<td>20/8</td>
<td>36/15</td>
<td>11/0</td>
<td>P = .035&lt;sup&gt;e&lt;/sup&gt;, P = .005&lt;sup&gt;c&lt;/sup&gt;, P = ns&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>ALS phenotypes: classic/bulbar/flail arm/flail leg/pyramidal/respiratory/PLMN/PUMN (No. of patients)</td>
<td>68/7/0/0/0/15/0</td>
<td>25/2/0/0/0/0/0</td>
<td>34/5/0/0/0/12/0</td>
<td>9/0/0/0/0/2</td>
<td>P = ns&lt;sup&gt;d&lt;/sup&gt;, P = ns&lt;sup&gt;d&lt;/sup&gt;, P = .047&lt;sup&gt;d&lt;/sup&gt;, P = .099&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>El Escorial-revised, categories: definite/probable/possible (No. of patients)</td>
<td>22/36/32</td>
<td>12/14/2</td>
<td>8/18/25</td>
<td>2/4/5</td>
<td>P = ns&lt;sup&gt;d&lt;/sup&gt;, P = .002&lt;sup&gt;b&lt;/sup&gt;, P = ns&lt;sup&gt;d&lt;/sup&gt;, P = .001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ODI (median) (IQR) (mo)</td>
<td>10.07 (6.08–19.27)</td>
<td>9.18 (6.08–14.32)</td>
<td>11.73 (6.23–19.53)</td>
<td>8.97 (4.07–19.27)</td>
<td>P = ns&lt;sup&gt;d&lt;/sup&gt;, P = ns&lt;sup&gt;d&lt;/sup&gt;, P = ns&lt;sup&gt;d&lt;/sup&gt;, P = .002&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ALSFRS-r (median score) (IQR)</td>
<td>38 (34–42)</td>
<td>34 (31–37)</td>
<td>40 (35–43)</td>
<td>40 (38–43)</td>
<td>P = .001&lt;sup&gt;e&lt;/sup&gt;, P = ns&lt;sup&gt;d&lt;/sup&gt;, P = .001&lt;sup&gt;f&lt;/sup&gt;, P = .002&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Progression rate (median) (IQR)</td>
<td>0.83 (0.45–1.38)</td>
<td>1.26 (0.68–2.84)</td>
<td>0.70 (0.29–1.20)</td>
<td>0.80 (0.45–1.12)</td>
<td>P = .022&lt;sup&gt;e&lt;/sup&gt;, P = .002&lt;sup&gt;b&lt;/sup&gt;, P = .008&lt;sup&gt;e&lt;/sup&gt;, P = ns&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Long/short survivors (No. of patients)</td>
<td>26/64</td>
<td>3/25</td>
<td>17/34</td>
<td>6/5</td>
<td>P = ns&lt;sup&gt;d&lt;/sup&gt;, P = .032&lt;sup&gt;b&lt;/sup&gt;, P = .008&lt;sup&gt;e&lt;/sup&gt;, P = ns&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Survival time from symptom onset to composite outcome (median) (estimated median) (95% CI) (mo)</td>
<td>46.63 (37.95–55.33)</td>
<td>34.5 (22.39–46.63)</td>
<td>46.63 (35.4–57.87)</td>
<td>72.73 (42.98–102.47)</td>
<td>P = .043&lt;sup&gt;b&lt;/sup&gt;, P = .004&lt;sup&gt;e&lt;/sup&gt;, P = .017&lt;sup&gt;c&lt;/sup&gt;, P = .001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Note:**—ns indicates not significant; PLMN, prevalent lower motor neuron; PUMN, prevalent upper motor neuron.

<sup>a</sup> Group differences in the demographic and clinical variables were evaluated using a Mann-Whitney U test for continuous variables and χ² tests for discrete variables. Log-rank tests were used to test for differences in survival between different radiologic clusters.

<sup>b</sup> Cluster 1 versus cluster 2.

<sup>c</sup> Cluster 1 versus cluster 3.

<sup>d</sup> Cluster 2 versus cluster 3.

outcome at the censoring date (Table). The short survivors’ group was characterized by 64 patients with a median time of observation of 36 months (IQR = 24–52 months), and all of them reached the composite outcome. Patients in cluster 1 showed a 4- and 10-fold risk of belonging to the short survivors’ group compared with those in clusters 2 and 3, respectively (P = .036 with hazard risk: 4.17 and a 95% CI, 1.11–15.87 and P = .007 with hazard risk: 10 and a 95% CI, 1.85–52.63, respectively).

Kaplan-Meier survival curves revealed that patients with ALS in cluster 1 showed a worse prognosis compared with patients in cluster 2 (log-rank: 4.10, P = .043) and cluster 3 (log-rank: 8.22 P = .004). No significant differences in overall survival from the onset of symptoms were detected between patients in these latter 2 groups (Table and Fig 2).

**DISCUSSION**

In the present study, we performed a data-driven analysis to identify the radiologic clustering of newly diagnosed patients with ALS, in relation to 3 well-known neuroanatomic loci involved in ALS disease, namely the PreCT<sup>22</sup> and ParaCT<sup>22</sup> and the medulla oblongata. Our data suggested that already at the time of diagnosis, patients with ALS showed specific patterns of neurodegeneration, with a prevalent impairment of the motor and extramotor cortex, cluster 3; MOv, cluster 2; or all 3 MR imaging measures, cluster 1. This latter group of patients was characterized by older age, higher female prevalence, greater disease severity expressed by lower ALSFRS-r scores, a higher progression rate, and lower median survival.

MR imaging data-driven approaches potentially have several advantages in clinical practice because they do not require a previous integration of clinical data. Unlike in interesting previous studies that first applied this approach, we focused our cluster-based analysis on CNS-selected areas that are already found in studies that first applied this approach,26,27 we focused our cluster-based analysis on the motor cortical areas and medulla oblongata, we first found that a considerable proportion (57%) of patients with ALS (belonging to cluster 2) showed greater involvement of the medulla already at the time of diagnosis. Second, a small subgroup of the ALS cohort (cluster 3, 12%) had early involvement of the motor and extramotor cortices with relative preservation of the medulla oblongata. Finally, 31% of those with ALS (cluster 1) showed wider and more prominent involvement of both cortical regions and medulla oblongata volume. These results appear in line with previous neuropathologic and neuroradiologic studies. Indeed, the earlier brainstem involvement found in 88% of our patients (clusters 1 and 2)
agrees with the findings of Brettschneider et al,41 who reported that brainstem involvement represents “stage 1” in ALS pathology. Nonetheless, the early involvement of cortical motor neurons with subsequent spread along contiguous neuroanatomic regions in fewer patients (43% belonging to clusters 1 and 3) may support the role of these brain regions in the onset of ALS disease, as recently postulated by a radiologic study of Schito et al.42 Finally, to explain the simultaneous and early involvement of both cortical regions and the medulla oblongata volume in patients with ALS in cluster 1, we referred to the most accredited model of ALS disease propagation reported in the literature.43 Indeed, also in these latter patients, the onset of the disease could have been focal in the cortical and/or the brainstem motor neurons, as postulated by Ravits,43 but a rapid spread of the disease along the neuroaxis would not allow us to detect the first neuroanatomic region involved, even at the onset of the disease in these patients. Alternatively, the onset of disease could have been due to “multifocal hits” with simultaneous involvement of cortical and brainstem motor neurons as recently postulated and demonstrated through an elegant neurophysiologic study by Sekiguchi et al.44

In addition, we observed that patients with ALS with wider impairment of both cortical and medulla oblongata regions (cluster 1) were characterized by an older age at onset and higher female prevalence. The effect of both age at onset and sex on MR imaging metrics was previously and extensively reported.37,45–47 On the basis of previous literature data, older age at symptom onset might provide a vulnerable substrate for faster and more severe disease propagation,46 while ALS sex-related brain functional and structural changes have been reported with controversial results.37,48

According to a very recent study, there is increasing evidence that ALS disease follows different patterns of neurodegeneration that are age- and sex-specific. Tan et al27 found a cluster of patients with ALS characterized by predominant involvement of the PreCT, younger age, and higher male prevalence. In addition, the authors described another cluster characterized by female prevalence and older age with wide posterior cingulate, parietal, cerebellar motor, temporal, and corpus medullare neurodegeneration.27 Overall, all these findings agreed with a previous population-based study that reported the interaction between age and female sex, with women more affected than men at older ages.49

The most intriguing findings of our study were the clinical consequences of the radiologic clustering of patients with ALS. Indeed, patients with ALS in cluster 1 with a wider impairment of both cortical and medulla oblongata regions were characterized by overall higher disease severity (expressed as lower scores of the total ALSFRS-r score), higher progression rate, and worse outcome, compared with patients in clusters 2 and 3. As stated above, several previous studies have underlined how PreCT, ParaCT and MOv could be used singularly as indicators of ALS disease aggressiveness.14,17,20,21,40 Nevertheless, these latter approaches relied invariably on the interpretation of clinical data that could somehow be misleading. An example of this limitation was recently aroused by Ferrea et al,25 who demonstrated through a discriminant analysis that patients with ALS with prevalent upper and lower motor neuron impairment could be differentiated by specific MR imaging metrics of the motor and extramotor regions. However, the same authors reported that the clinical distinction between ALS phenotypes (prevalent upper and prevalent lower motor neurons and classic ALS) is somewhat heterogeneous; therefore, they included this concept as a limit of their study.25 Instead, using a cluster-based approach without a priori clinical categorization of patients with ALS, we overcame the
intrinsie limitation of investigating the correlation between clinical characteristics and each neuroanatomic structure, and we demonstrated that both the impairment of cortical and medullar regions corresponded simultaneously with the severity, rate of progression, and survival in ALS disease. Furthermore, a data-driven analysis could also overcome the potentially subjective interpretation of reported symptoms, which could be biased by “recall error,” especially in patients with a long-lasting disease.

The main limitation of our study is the lack of a longitudinal MR imaging analysis, which, instead, would have better defined the trajectories of the disease burden and the rate of decline of MR imaging metrics according to different clusters. Another limitation is the lack of neuropsychological assessment, which would guarantee a better characterization of cognitive profiles among radiologic clusters. Last, in our study, we included only patients with a definite, probable, or possible diagnosis of ALS. The inclusion of patients with ALS with pure lower motor neuron impairment, as well as progressive muscular atrophy or progressive lateral sclerosis, may be of potential interest to evaluate whether these subtypes segregate from ALS on the basis of their radiologic profiles.10–12

CONCLUSIONS

We demonstrated that radiologic clustering of newly diagnosed patients with ALS could have clinical and prognostic implications and could unravel some aspects of the extreme phenotypic heterogeneity of ALS disease. Patients with undoubtedly more advanced and extended disease burdens (cluster 1) should be carefully evaluated to propose therapeutic interventions, such as timely positioning of percutaneous endoscopic gastrostomy or tracheostomy.

ACKNOWLEDGMENT

We are grateful to the patients with ALS and their families.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Comparison between Dual-Energy CT and Quantitative Susceptibility Mapping in Assessing Brain Iron Deposition in Parkinson Disease

Y. Chen, M. Ge, J.J. Kang, Y.C. Ding, Y.C. Chen, and Z.Z. Jia

BACKGROUND AND PURPOSE: Both dual-energy CT and quantitative susceptibility mapping can evaluate iron depositions in the brain. The purpose of this study was to compare these 2 techniques in evaluating brain iron depositions in Parkinson disease.

MATERIALS AND METHODS: Forty-one patients with Parkinson disease (Parkinson disease group) and 31 age- and sex-matched healthy controls (healthy control group) were included. All participants underwent brain dual-energy CT and quantitative susceptibility mapping. ROIs were set bilaterally in the globus pallidus, substantia nigra, red nucleus, caudate nucleus, and putamen. CT values and magnetic susceptibility values were obtained in each ROI. Differences in CT values and magnetic susceptibility values between the Parkinson disease and healthy control groups were compared, followed by analysis of receiver operating characteristic curves. Correlations between CT values and magnetic susceptibility values were then evaluated.

RESULTS: The CT values of the bilateral globus pallidus, substantia nigra, and red nucleus were higher in the Parkinson disease group (P < .05). The magnetic susceptibility values of the bilateral globus pallidus and substantia nigra were higher in the Parkinson disease group (P < .05). The CT value of the right globus pallidus in linear fusion images had the highest diagnostic performance (0.912). Magnetic susceptibility values of the bilateral globus pallidus in the Parkinson disease group were positively correlated with CT values at the level of 80 kV(peak), linear fusion images, and SN150 kV(p) (r = 0.466–0.617; all, P < .05).

CONCLUSIONS: Both dual-energy CT and quantitative susceptibility mapping could assess excessive brain iron depositions in Parkinson disease, and we found a positive correlation between CT values and magnetic susceptibility values in the bilateral globus pallidus.

ABBREVIATIONS: AALv3 = Anatomical Automatic Labeling Version 3; AUC = area under curve; CA = caudate nucleus; DECT = dual-energy CT; GP = globus pallidus; HC = healthy control; MNI = Montreal Neurological Institute; MSV = magnetic susceptibility values; PD = Parkinson disease; PU = putamen; QSM = quantitative susceptibility mapping; RN = red nucleus; ROC = receiver operating characteristic; SN = substantia nigra

Parkinson disease (PD) is a neurodegenerative disease that causes progressive death of dopaminergic neurons, with excessive iron deposition within the nigrostriatal system being a main factor.1–3 Therefore, assessment and monitoring of iron deposition in the brain are particularly vital for patients with PD. Both postmortem investigations and animal studies have confirmed the correlation between brain iron deposition and magnetic susceptibility.4 Quantitative susceptibility mapping (QSM), a newly developed MR imaging technique, is based on the correspondence between phase data and the magnetic field, which can quantitatively assess brain iron deposition by measuring magnetic susceptibility values (MSV). Some studies have demonstrated brain iron accumulation in patients with PD by QSM to validate QSM as a method of tracking brain iron, which can be used as a biomarker and therapeutic target for the disease.5–7 Thus, QSM can be used as a guide in the early diagnosis of PD.

However, as an fMRI technique, QSM has some limitations in its application. Therefore, to address this problem, dual-energy CT (DECT) has recently been introduced. DECT has the ability to simultaneously capture images at different energy levels, creating the potential to gauge iron deposition without the disadvantages of energy-dependent CT attenuation of tissue.8–11 Furthermore, the continuous development of CT reconstruction algorithms and detector technology has helped to significantly reduce the radiation dosage, making CT quicker and safer.8–12
Demographics and clinical status of the study participants

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (mean) (yr)</th>
<th>Disease Duration (mean)</th>
<th>H-Y (Stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with PD</td>
<td>65.0 (SD, 7.5)</td>
<td>4.5 (SD, 2.7)</td>
<td>1.9 (SD, 1.1)</td>
</tr>
<tr>
<td>HCs</td>
<td>62.4 (SD, 7.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** H-Y indicates Hoehn and Yahr stage.

Few studies have combined these imaging techniques to explore the relationship between CT values and the MSV of paramagnetic substances such as iron in the brain. Previous studies have demonstrated the efficiency of DECT in measuring liver iron, and a recent study found that it was possible to estimate CT values using QSM of the brain. Therefore, we hypothesized that CT values from DECT could assess QSM-based MSV when measuring brain iron deposition and that these 2 parameters may be correlated in patients with PD.

**MATERIALS AND METHODS**

**Study Population**

This study was approved by the Ethics Committee of Nantong University Affiliated Hospital. All participants provided written consent as required by institutional guidelines. We selected 52 patients from a cohort of patients with clinically proved PD receiving treatment in our hospital from October 2020 to December 2021. After we applied inclusion and exclusion criteria, 41 eligible patients (PD group, 23 men; average age, 63.96 [SD, 8.27] years; 18 women; average age, 66.28 [SD, 6.47] years) were included. In addition, 31 age- and sex-matched healthy controls (HC group) were recruited. Their clinical characteristics are summarized in the Table. All participants underwent DECT and QSM. The interval between DECT and the MR imaging examination was <1 week.

The inclusion criteria were as follows: 1) Patients must have been diagnosed by a neurologist according to PD diagnostic criteria; 2) patients underwent DECT and QSM; 3) patients had no history of brain surgery; 4) patients had not received iron supplementation (eg, blood products, ferrous citrate, and so forth) or any dopamine medication within 1 week of testing; and 5) patients had no concurrent diseases that could lead to abnormal iron deposition (eg, intracerebral hemorrhage, renal failure, cerebral infarction, amyotrophic lateral sclerosis, and so forth) and no increased gastrointestinal iron absorption.

The exclusion criteria were as follows: 1) incomplete imaging data, which excluded 9 participants; 2) image artifacts, which excluded 2 participants due to motion artifacts.

**DECT Scan**

Participants underwent a third-generation DECT head scan (Somatom Force; Siemens). The dual-energy mode was run in different kilovolt settings (tube A: 80 kVp[peak]; tube B: Sn150 kVp[p]) with a dual energy scanning scheme (rotation time, 1.0 second; pitch, 0.7; layer thickness, 5 mm; layer spacing, 1 mm; collimation, 64 × 0.6 mm; FOV, 200 mm; volume CT dose index, 27.72 mGy). By means of automatic attenuation-based tube current modulation, the cross-sectional images were reconstructed using a kernel (Qr40; Siemens) (layer thickness, 1.0 mm; layer spacing, 0.7 mm).

A linear virtual hybrid image was generated by simulating a standard 120 kV(p) data set with a linear combination of the originally acquired 80-kV and Sn150-kV(p) image data. Final images with high and low kilovolts and their linear fusion were derived.

**MRI**

A 3T MR imaging scanner (Signal 750w; GE Healthcare) with a 24-channel head matrix coil was used to obtain MR images. Foam pads and earplugs were used to prevent head movement and reduce scanner noise. The QSM sequence was based on the gradient-echo sequence for multivoxel cross-sectional scans. The scan parameters of QSM were as follows: TR/TE, 32.5/3.3 ms; flip angle, 20°; layer thickness, 1 mm; acceptance bandwidth, 62.50 Hz/Px; FOV, 256 × 256 mm; matrix, 256 × 256 mm; imaging time, 3 minutes 42 seconds. The scan range of QSM was the substantia nigra (SN) area and the basal ganglia area, symmetric on both sides. Influences of the skull base, sinus gas, skull, blood vessels, and CSF were avoided to the greatest extent. Scanning started when the automatic shimming reached >98% of the half-height line width. In addition, routine brain scans were obtained before QSM to rule out various brain diseases.

**Data Acquisition and ROI Extraction**

MR imaging data were analyzed using Matlab R2019a (Version 9.6.0; MathWorks). QSM images were generated using the STI Suite toolbox (https://people.eecs.berkeley.edu/~chunlei.liu/software.html, Version 3.0) reconstruction. Image alignment and normalization of MR images were performed in SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). Alignment of CT and MR images was performed using 3D Slicer software (Version 4.10.2; http://www.slicer.org), and processing was handled automatically by the program.

Image processing included the following 5 steps (Fig 1):

1) QSM reconstruction: Enhanced T2*-weighted angiography sequence images consisted of a magnitude map and a phase map. After we imported ESWAN into the STI Suite, the corresponding amplitude and QSM maps were generated after decoherence.

2) MR image normalization: The magnitude map was aligned with the T1 structure image to generate T1-cor. The magnitude map was then aligned with the corresponding structural image position. The T1-cor was normalized and aligned to the Montreal Neurological Institute (MNI) standard space to generate T1-MNI, and the transformation function (T-matrix) in this normalization process was recorded.

3) DECT image normalization: The DECT images were aligned with T1-cor, performing exactly the same transformation as T1-MNI aligned to the standard space.

4) QSM normalization: The T-matrix was applied to transform the QSM to the MNI standard space.

5) ROI extraction: After we matched the normalized MRI, QSM, and CT images with the Anatomical Automatic Labeling Version 3 (AALv3) template, we extracted the MSVs and CT values (average values) of the corresponding 3D ROIs.

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extracted ROIs were set bilaterally in the globus pallidus (GP), SN, red nucleus (RN), caudate nucleus (CA), and putamen (PU) (Fig 2).

**Statistical Analysis**
The Kolmogorov-Smirnov test was applied to check the normality of each set of data. The mean (SD) was used to represent normally distributed data. The t test was used to compare differences in CT values and MSVs between the PD and HC groups. Receiver operating characteristic (ROC) curves were implemented to assess the diagnostic performance for PD. The Pearson correlation analysis was used to evaluate correlations between CT values and MSV for data with normal distributions. The false discovery rate was used to correct P values for multiple comparisons, and P < .05 was considered statistically significant. Statistical analyses were performed using SPSS 25.0 (IBM).

**RESULTS**

**Participant Demographics**
There were no significant differences in age or sex between the PD and HC groups (both, P > .05; Table).

**Differences in CT Values and MSV between the PD and HC Groups**
The CT values of the bilateral GP, SN, and RN were significantly higher in the PD group than in the HC group (all P < .05; Online Supplemental Data). The MSV of the bilateral GP and SN were significantly higher in the PD group than in the HC group (all, P < .05; Online Supplemental Data). However, there were no significant differences in CT values and MSV between the 2 groups in other ROIs (Fig 3).

**ROC Curve Analysis of CT Values and MSV for Diagnosing PD**
The ROC curve analysis showed that the CT values in the bilateral GP, SN, and RN at the level of 80 kV(p), linear fusion images, and Sn150 kV(p) could distinguish the PD group from the HC group (all, P < .05). The area under curve (AUC) of CT values was highest for the right GP in the linear fusion images (0.912).

The ROC curve analysis showed that the MSV in the bilateral GP and SN could distinguish the PD group from the HC group (all P < .05). The MSV of the right SN had the highest AUC (0.732) (Fig 4 and Online Supplemental Data).
Correlations between CT Values and MSV in the PD Group

MSV of the left GP in the PD group were positively correlated with CT values at the levels of 80 kV(p), linear fusion images, and Sn150 kV(p) ($r = 0.617, P < .001$; $r = 0.563, P < .001$; $r = 0.511, P < .001$). MSV of the right GP in the PD group were positively correlated with CT values at the levels of 80 kV(p), linear fusion images, and Sn150 kV(p) ($r = 0.550, P < .001$; $r = 0.524, P < .001$; $r = 0.466, P = .002$). There were no correlations between CT values and MSV in the PD group in other ROIs (Fig 5 and Online Supplemental Data).

DISCUSSION

Studies have shown that iron metabolism is present during the aging process in healthy participants, while abnormal iron deposition has been observed in some neurodegenerative diseases.\textsuperscript{14,15} QSM is the most commonly used method for MR imaging of iron quantification. Some previous studies used QSM to quantitatively assess iron deposition in the brains of patients with PD, not only for early detection and diagnosis but also for assessing neurologic impairment of cognitive and motor function and guiding neurosurgical treatment, making it a feasible noninvasive test for PD.\textsuperscript{7,16–22} Although MR imaging has advantages in iron quantification for patients with high iron content, previous studies have shown that its signal decays rapidly with increasing iron concentration. High iron content can indirectly lead to inaccuracies in the subsequently generated magnetization maps due to transverse signal attenuation and the possibly insufficient number of measurements. Moreover, MR
imaging is expensive, with long scan times and some contraindications. Therefore, finding an alternative quantification method is necessary. Previous studies have investigated the accuracy of DECT for quantifying liver iron content. DECT provides a simple and easy method for iron quantification with diagnostic performance similar to that of MR imaging. Therefore, we aimed to explore and compare the use of DECT and QSM for measuring iron deposition in the brain in patients with PD and to verify whether DECT could be a cost-saving and alternative method for examining patients with PD.

DECT is performed by a weighted linear combination of 2 acquisition images (80 kV[p] and Sn150 kV[p]) to generate a dual-energy-simulated standard CT images can have the characteristics of standard 120 kV(p) images in terms of pixel noise and CT values. Thus, the dual-energy-simulated standard CT images can be used alternatively for diagnosis. Compared with MR imaging, CT is widely used due to lower cost, shorter examination time, and relatively simple image acquisition methods. Furthermore, DECT is effective for patients with possible motor impairment and metal dentures.

In the present study, the MSV of the bilateral GP and SN were found to be apparently higher in the PD group than in the HC group, suggesting that patients with PD had increased iron deposition in these regions. Guan, Chen and Lewis et al found that MSV from QSM in patients with PD were significantly higher than those in healthy patients in the GP, RN, SN, and thalamus. These findings were consistent with the pathogenesis of PD and in agreement with the results of the present study. However, the present study measured not only the MSV in these regions but also CT values from DECT. Our results demonstrated that the CT values of the PD group in the GP, SN, and RN at 80 kV(p), linear fusion, and Sn150 kV(p) were higher than those in the HC group, indicating that increased iron deposition in these regions led to elevated CT values. The CT values and MSVs of different ROIs had a different diagnostic efficacy for PD. The area under the ROC curve of the CT values of the linear fusion images in the right GP and the AUC of the MSV in the right SN were significantly higher than in other ROIs. It is possible that this finding is because the main lesional areas in PD are the SN and GP. Unlike previous studies, the present study measured CT values from DECT to complement the diagnostic performance of QSM. We also performed a correlation analysis between MSV and CT values at different levels in patients with PD. At 80 kV(p), linear fusion, and Sn150 kV(p), the CT values detected in the bilateral GP were positively correlated with the MSV.

The GP is the most iron-rich structure in the brain, and patients with PD have increased iron deposition in the GP. Because iron (ferritin and hemosiderin) is paramagnetic, it can cause local magnetic field inhomogeneity, resulting in an increase in MSVs. At the same time, as a metal, iron can also lead to an increase in CT values. In addition, by using DECT scanning, we found that a smaller kilovolt (peak) led to better correlation and greater tissue attenuation at a low kilovolt (peak) compared with a high kilovolt (peak), leading to higher CT values. Thus, larger differences in tissue contrast improved the correlation between CT values and MSV. This evidence provided the basis for subsequent low-dose studies. There was no strong increase in susceptibility within the GP of patients with PD compared with the SN. Although calcification of the GP leads to negative magnetization in QSM, this may be overlooked due to the strong paramagnetic properties of iron. Previous studies have shown that iron is usually distributed in the anterior part of the GP externus; however, the present study targeted the entire GP, contradicting former research on the iron content of the GP.

Previously, increased iron deposition in the SN was studied as the most representative pathologic feature in patients with PD. Still, no correlation between MSV and CT values of the SN was found in the present study, which may be related to the specific site of iron deposition in the SN, because iron often accumulates...
in the dorsal-caudal region and the SN is very small. Another factor that should not be overlooked is the comparatively smaller sample size. Thus, when one quantifies the magnetic induction intensity of the whole SN, the results here may be biased. This issue could explain why there was no correlation between MSV and CT values in the SN.

A previous study by Dimov et al. found that the MSV of bone correlated with CT values due to the antimagnetic susceptibility and high CT values from calcification. Although abnormal iron deposition has also been observed in several deep brain nuclei in other studies, we found no correlation between MSV and CT values in the CA, PU, and RN. This could be the result of low iron deposition and the absence of calcification in these regions, causing the amount of iron deposited at these sites to be insufficient to produce a correlation, in agreement with previous findings. Future studies are needed to thoroughly evaluate these sites.

In this study, DECT and QSM were equivalent in objectively assessing brain iron deposition in patients with PD. There was a positive correlation between MSVs and CT values of the GP. These results suggest that both DECT and QSM can detect brain iron deposition. In most cases, QSM remains the technique of choice to be used to measure brain iron deposition. Moreover, with the development of new technologies, the amount of radiation exposure is decreasing. Thus, QSM and CT could substitute for each other in evaluating iron deposition in the brain. It is beneficial to provide different imaging options for patients that can provide an essential reference for the clinical diagnosis of PD.

There were several limitations to the present study. First, the small sample size may lead to uncertainty in the analysis. However, our participants would have received radiation doses as a result of the CT examinations. Second, other metals may also contribute to an increase in MSV, though these effects are weaker than those of iron.

CONCLUSIONS

The present study showed increased brain iron deposition in patients with PD using DECT and QSM imaging analyses. MSV correlated with CT values in the bilateral GP, suggesting that DECT and QSM are equally valuable for assessing brain iron deposition and can be used interchangeably.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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ABSTRACT

BACKGROUND AND PURPOSE: Incidental findings are discovered in neuroimaging research, ranging from trivial to life-threatening. We describe the prevalence and characteristics of incidental findings from 16,400 research brain MRIs, comparing spontaneous detection by nonradiology scanning staff versus formal neuroradiologist interpretation.

MATERIALS AND METHODS: We prospectively collected 16,400 brain MRIs (7782 males, 8618 females; younger than 1 to 94 years of age; median age, 38 years) under an institutional review board directive intended to identify clinically relevant incidental findings. The study population included 13,350 presumed healthy volunteers and 3250 individuals with known neurologic diagnoses. Scanning staff were asked to flag concerning imaging findings seen during the scan session, and neuroradiologists produced structured reports after reviewing every scan.

RESULTS: Neuroradiologists reported 13,593/16,400 (83%) scans as having normal findings, 2193/16,400 (13.3%) with abnormal findings without follow-up recommended, and 614/16,400 (3.7%) with “abnormal findings with follow-up recommended.” The most common abnormalities prompting follow-up were vascular (263/614, 43%), neoplastic (130/614, 21%), and congenital (92/614, 15%). Volunteers older than 65 years of age were significantly more likely to have scans with abnormal findings (P < .001); however, among all volunteers with incidental findings, those younger than 65 years of age were more likely to be recommended for follow-up. Nonradiologists flagged <1% of MRIs containing at least 1 abnormality reported by the neuroradiologists to be concerning enough to warrant further evaluation.

CONCLUSIONS: Four percent of individuals who undergo research brain MRIs have an incidental, potentially clinically significant finding. Routine neuroradiologist review of all scans yields a much higher rate of significant lesion detection than selective referral from nonradiologists who perform the examinations. Workflow and scan review processes need to be carefully considered when designing research protocols.

ABBREVIATIONS: CHS = Cardiovascular Health Studies; NPV = negative predictive value; PI = principal investigator; PPV = positive predictive value; SE = standard error
population-based cohorts across narrow age ranges, and specialty MRI protocols limiting external validity and/or having problem-
atic methods for identifying incidental findings.2-6

There is poor consensus on whether the baseline prevalence of clinically significant brain abnormalities in the general popu-
lation justifies the routine use of neuroradiologists to review research MRIs. Standard practices for research MRI interpreta-
tion differ by institution and by country, but budgetary and workflow constraints have historically limited expert review
solely to scans flagged by scanning technologists and research personnel. These nonradiologists have variable experience and,
in most circumstances, lack formal training in diagnostic MR imaging reporting; nonetheless, they are tasked with screening and referring concerning findings for further review, leaving
most scans without formal interpretation.

In this prospective cross-sectional study, we describe the prev-
ance and characteristics of incidental findings and assess the
detection rate of abnormalities of nonradiologists compared with
neuroradiologists from a series of 16,400 consecutive research brain MRIs collected at a single institution across 18 years.

MATERIALS AND METHODS
All research activities performed and described were conducted in
accordance with an institutional review board–approved protocol
at the University of Wisconsin-Madison.

Population Recruitment and Inclusion
Brain MRIs were collected from 17,010 consecutive volunteers
from research studies conducted at the University of Wisconsin-
Madison from April 2002 to March 2020. The final study population
included 16,400 scans (7782 males, 8618 females; younger
than 1 year of age to 94 years; median age, 38 years) after excluding
610 whose participant intake forms lacked age and/or sex.
The overall study data base compiled neuroimaging from volun-
teeers in >300 research protocols and 73 principal investigator
(PI) groups. All volunteers or their guardians provided informed
consent before participation. Participants were recruited by each
individual PI on the basis of eligibility criteria for their respective
studies. Most studies recruited healthy age-matched control vol-
unteers, while a minority recruited individuals with pre-existing
conditions such as stroke, MS, and dementia.

Each scan was treated as a unique case, though some partici-
ants were scanned more than once. We are unable to quantify
how many participants were serially scanned because of the
research scan anonymization, a code that sometimes changed
with time for the same individual. Typical workflow required that
all scans be read unless a prior MRI in the same protocol had
been read within the past year, in which case the PI was not
required to submit the scan for radiologist interpretation. We
encountered significant abnormalities on follow-up scans in
some previously healthy subjects, justifying review of new studies.
Most important, volunteers with known pre-existing medical
conditions, including those with disease-related neuroimaging
findings, were not excluded. Therefore, volunteers with known
conditions were considered to have either normal or abnormal
findings, or no follow-up was recommended unless other previ-
ously unknown brain abnormalities were discovered. If a
volunteer had previously been informed of a clinically significant
finding and this was seen again at follow-up, this duplicate was
placed in the “abnormal, no follow-up” category unless there had
been clear-cut interval worsening. Volunteers with normal anat-
omic variants and common incidental findings of doubtful sig-
nificance were categorized as having normal findings.

Brain MRI Acquisition and Analysis
MRIs were performed on GE Healthcare MRI scanners at multi-
ple research sites. Most scans were performed at 3T (15,888/
16,400, 97%). Each PI chose pulse sequences on the basis of indi-
vidual study needs, leading to a heterogeneous variety of scan
protocols. Virtually all included T1-weighted images (mostly vol-
umetric acquisitions) and additional sequences were included for
most protocols, particularly in those older than 45 years of age
for aging and dementia research. Examinations containing brain
anatomy and already postprocessed parameter maps (eg, perfu-
sion if available) were sent to the PACS for neuroradiologist
interpretation. Advanced imaging techniques and raw data files
including PET, 4D flow MRA, fMRI, and diffusion tensor maps
were not interpreted.

MRI Interpretation and Reporting
Nonradiologists including scanning staff (MRI technologists and
nurses) and research personnel (PhD scientists and neuropsychol-
gists) were instructed to document concerns at the time of scan-
ing using the same Web-based intake form they had used to
upload cases to the reading queue of neuroradiologists. All scan-
ing technicians were certified for MRI safety and technical profi-
ciency, as verified by more senior technicians and ultimately the
PI. The technicians in our neuroscience centers were specialty
research personnel, most without a radiologic technologist degree,
typically with 3–15 years of experience. The technicians in our
combined clinical/research site were mostly formally certified
radiologic technologists with 2–20 years of experience. Excluding
the 202/16,400 scans for which scanner location was unspecified
on the intake form, 9944/16,198 (61%) scans were obtained on
scanners designated for research only, while 6254/16,198 (39%)
scans were acquired on clinical scanners. All scans were anonym-
ously coded, sent to the PACS, and formally interpreted by a
neuroradiologist. Intake forms provided readers with volunteers’
age and sex, study diagnosis, and known medical conditions. Each
neuroradiologist (H.A.R. with >30 years of experience, A.S.F. with
>20 years of experience; V.P. with >20 years of experience, L.E.W.
with >10 years of experience) independently reviewed scans and
generated reports using a structured form linked to the volunteer’s
research examination on the PACS (Online Supplemental Data).
In each report, the neuroradiologist classified each examination
finding as 1) normal, 2) abnormal, no follow-up, or 3) abnormal,
follow-up recommended.

Our main aim while categorizing scans was to identify the full
range of incidental findings in our population, but to only recom-
mand follow-up for potentially clinically significant abnormalities.
A clinically significant abnormality was defined as an unexpected
MRI finding the radiologist considered serious enough to prompt
notification of the research subject and review by their medical
practitioner. Trivial changes, normal variants, and lesions within
Follow-up on Incidental Findings

All volunteers or their guardians signed informed consent/assent under an institutional review board–approved protocol in which they addressed disclosure of incidental findings. On categorizing a scan as abnormal, follow-up recommended, the neuroradiologist informed the PI team, who unblinded the file and referred to the volunteer’s informed-consent document to determine the volunteer’s preference. The lead investigator would either directly communicate the finding to the volunteer, ask the neuroradiologist to contact the volunteer to disclose the findings, or respect the wishes of the volunteer not to be informed of incidental findings. All clinically relevant findings were communicated to both the participant and his or her physician if requested.

Statistical Analysis

After we acquired and interpreted 17,010 brain MRIs, those without documented age and/or sex were excluded, resulting in a final study population of 16,400. Examinations marked abnormal with follow-up recommended were further subcategorized on the basis of abnormality type using information in each structured report (Online Supplemental Data).

Descriptive Statistical Analysis

Most variables are either categoric or binary. Variables are summarized by the percentage of volunteers in each group. Correlations between categoric or binary variables were evaluated using $\chi^2$ tests. Continuous variables are presented as mean (SD) and compared using ANOVA for multiple groups and the Student t test for 2 groups. The association between scans with abnormal findings and those with normal findings was determined by univariate logistic regression adjusted for age and sex. All analyses were performed using R statistical and computing software (Version 3.5.2; http://www.r-project.org/), and P values < .05 were considered statistically significant.

We compared written initial concerns by nonradiologist reviewers with the neuroradiologist’s scan classification. Our other descriptive analyses divide scans with abnormal findings on the basis of whether follow-up was recommended; however, this analysis treated all scans with abnormalities as 1 classification because we intended to determine the ability of nonradiologist reviewers to classify scans as having abnormal–versus-normal findings on the basis of whether they perceived at least 1 incidental finding to be present or absent, respectively. Initial concerns were considered relevant to the analysis if they described a presumptive abnormality (eg, “cyst,” “meningioma”) and were excluded if it listed known lesions or these were irrelevant (eg, “subject motion,” “anxiety meds given before scan”). Relevant initial concerns were compared with the final neuroradiologist classification (normal versus abnormal) and were presented in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Inferential Statistical Analysis

An ordinal logistic regression model was constructed to investigate how sex and age affect scan classification. Results of this analysis are presented in log order with standard error (SE) and 95% CIs. An increase in log order represents an increased likelihood of a scan having abnormal findings if a given variable was present.

RESULTS

Study Characteristics

This study comprised 16,400 research volunteers enrolled in studies for which brain MRIs were acquired at the University of Wisconsin–Madison and included both typical volunteers (ie, those without previously identified intracranial abnormalities) as well as individuals with a known brain lesion or congenital predisposition to neuropathology detectable by imaging (eg, excess mineralization in trisomy 21). Study demographic characteristics are shown in Table 1.

Descriptive Results

In 16,400 consecutive brain MRI examinations from research volunteers, 13,593/16,400 (83%) had normal findings, 2193/16,400 (13.3%) had abnormal findings but no follow-up was recommended, and 614/16,400 (3.7%) had abnormal findings with follow-up recommended (Fig 1). Among the 3250 volunteers recruited due to a known medical condition, 1948/3250 (60%) had normal findings, 1149/3250 (35%) had “abnormal findings without follow-up recommended,” and 153/3250 (5%) had abnormal findings with follow-up recommended. Except as detailed below, changes commonly encountered in the general population were placed into the “normal/normal variant” category. This included paranasal sinus mucosal changes ($n = 2891$, 17.6%), prominent perivascular spaces ($n = 2857$,
17.4%), pineal cysts (n = 721, 4.4%), arachnoid cysts (n = 550, 3.4%), uncomplicated developmental venous anomalies (n = 509, 3.1%), and low cerebellar tonsils that did not meet the Chiari I malformation criteria (n = 358, 2.2%).

WM changes were assessed with each volunteer’s age and known risk factors in mind but were quantified only for some aging studies using the 10-point Cardiovascular Health Studies (CHS) score. Overall, 5089/16,400 (31%) volunteers were noted to have WM changes. Although most volunteers with WM changes were not prospectively scored using CHS methods, we retrospectively estimated that most volunteers (4116/5089, 81%) had mild disease (CHS 2–4). A minority (973/5089, 19%) had moderate-to-severe WM disease (CHS 5–9); of these patients, 95/5089 (2%) were considered to have abnormal findings with follow-up recommended to assess treatable vascular risk factors. Developmental venous anomalies were considered abnormal only if they showed adjacent parenchymal changes including gliosis or cavernoma.

Scans recommended for follow-up were subcategorized by 2 independent reviewers on the basis of the most concerning finding in each examination (Online Supplemental Data). Vascular pathologies were most common (43%), and of these, WM hyperintensities were the leading cause for referral. Examples of scans with abnormal findings with follow-up recommended are shown in Fig 2. A detailed breakdown of findings is found in the Online Supplemental Data.

Disclosure of Potentially Serious Abnormalities

Reports were released only for abnormal scans with follow-up recommended. With rare exceptions, volunteers in the abnormal, follow-up category were first informed by telephone. Most “cold calls” were made by one of the neuroradiologists (H.A.R.) who is also board-certified in neurology. Volunteers were provided a brief, written report containing selected images. Results, reports, and recommendations were communicated to the participant’s physician if requested in writing. Original data files were not released.

Abnormality Detection Analysis of Nonradiologists

Initial concerns at the time of scanning were noted for 133/16,400 (<1%) scans (Table 2). Overall, nonradiologists showed very low sensitivity to abnormalities, flagging only 52/2807 (2%) scans later considered to have abnormal findings by a neuroradiologist, regardless of whether follow-up was recommended. Among scans flagged by nonradiologists and confirmed to contain an abnormality, 22/52 (42%) contained an abnormality warranting further clinical evaluation. Therefore, nonradiologists detected 22/2807 (<1%) scans in which a clinically significant abnormality was confirmed and recommended for follow-up. Under the assumption that

FIG 1. Violin plots stratified by scan category. Boxplots within each plot have medians and interquartile ranges. The median age and interquartile range of volunteers with normal examination findings were 28 and 42 years, respectively. The median age and interquartile range of volunteers with abnormal examination findings for which follow-up was not recommended were 61 and 27 years, respectively. The median age and interquartile range of volunteers with abnormal examinations for which follow-up was recommended were 58 and 37 years, respectively.

FIG 2. Illustrative cases of incidental findings for which clinical follow-up was recommended. Case examples of the 3 most frequently encountered abnormality categories, lesions marked by arrows, all reportedly asymptomatic at the time of scan. A, Vascular: a 38-year-old participant with trisomy 21 and normal scan findings 2 years earlier and found to have bitemporal ischemic lesions, suspected to be cardioembolic versus Moyamoya vasculopathy (axial T2-FLAIR). B, Neoplastic: a 68-year-old participant with normal research scan findings 3 years earlier now has an infiltrative left parietal mass, later proven to be a glioblastoma (axial T2-FLAIR). C, Congenital: a 29-year-old participant with extensive left posterior Sylvian polymicrogyria (sagittal T1).
nonradiologist reviewers omitted comments if they considered a scan to have normal findings; nonradiologist reviewers demonstrated high specificity for examinations with normal findings (99%). Furthermore, nonradiologist reviewers demonstrated modest positive predictive value (39%) for examinations with confirmed abnormalities and good negative predictive value (83%) for examinations with normal findings.

**Inferential Analysis**

χ² tests for independence were performed to identify categoric variables significantly associated with scan category classification. The nominal level of significance α = .05 was used as a threshold for statistical significance. Sex was not significantly associated with category classification (P = .37), while age dichotomized as “younger than 65” and “65 or older” was associated with category classification (P < .001). The Cramer V statistic was computed to determine the effect size of this association (V = 0.16), indicating a small effect. The highly statistically significant result from the χ² test most likely results from sample size versus the effect of age on category classification.

An ordinal logistic regression model was constructed to understand how sex and age affect scan classification. Male volunteers were more likely to be classified as having normal findings than female volunteers (log odds = −0.201; SE = 0.07; 95% CI, −0.34 to −1.14). Considering those with abnormal findings, young volunteers (younger than 65 years of age) were more likely to be recommended for follow-up than volunteers older than 65 years of age (log odds = 1.014; SE = 0.06; 95% CI, 0.89−1.14).

**DISCUSSION**

Incidental findings are previously unknown abnormalities of potential clinical significance discovered on research brain examinations that are unrelated to the research study aims and distinct from a volunteer’s clinical history. There is significant public interest in knowing the baseline prevalence of brain abnormalities, yet routine screening of brain MRIs for asymptomatic individuals has not been recommended. Furthermore, it is unclear whether expert review of research brain imaging examinations is prudent or if, instead, nonradiologists can detect abnormalities to facilitate expert review. Therefore, in 2002, the neuroradiology section at the University of Wisconsin Department of Radiology implemented a system for documenting incidental findings in research brain MRIs. As part of this initiative, nonradiologists were instructed to report any concerns at the time of scanning before formal interpretation by a neuroradiologist.

Consistent with other studies examining incidental findings in research MRIs, our study found about 4% of volunteers had at least 1 potentially serious brain abnormality. In a study examining incidental findings in 1867 healthy young adults, a similar prevalence of potentially serious brain abnormalities was reported. However, we consider that the approach of the study for the detection of abnormalities was insufficient because some scans were screened only by nonexperts viewing only T1- and T2-weighted images; only after being flagged during this initial screening step would a scan undergo expert review by an experienced clinical neuroradiologist reviewing all acquired sequences. In contrast, in our study, every research volunteer underwent expert review of all sequences acquired per each specific study protocol.

Similar to the results of our study, an analysis of 2000 individuals older than 55 years of age from the Rotterdam Study (a prospective, population-based cohort study of age-related brain changes) found that the most common incidental findings were subclinical vascular pathologies and that the prevalence of abnormalities increased with age. In contrast, while potential malignancies represented roughly half of incidental findings in a meta-analysis of studies with incidental findings, in our study, neoplastic phenomena were found in only 21% of MRIs recommended for follow-up. This discrepancy may be due to the emphasis on aging research at our institution, which could bias results toward nonspecific, age-associated WM hyperintensities. The authors of the Rotterdam Study claimed that a major strength of their study was its uniform MRI protocol, which indeed strengthens its internal validity. However, our study has greater external validity because of the variety of brain MRI protocols used across studies at our institution as well as the age range from infancy to elderly, reflecting the realistic heterogeneity of research neuroimaging protocols.

This study also examined and compared detection rates of abnormalities for all brain MRIs between nonradiologist reviewers and neuroradiologists. We prospectively collected this information to estimate how a workflow system using a selective “flag and refer” approach would compare with the “read every scan” approach. Our study found that nonradiologists flagged <2% of scans containing abnormalities, regardless of whether follow-up was recommended. However, among scans flagged and later confirmed to contain an abnormality, 22/52 (42%) were recommended for further clinical evaluation, demonstrating a poor PPV (22/133, 0.16) for flagging scans containing abnormalities warranting further evaluation. Nonradiologists were more likely to detect large abnormalities of variable clinical significance (eg, cystlike lesions, ventriculomegaly) and miss subtle, potentially serious abnormalities (eg, aneurysms, infiltrative gliomas) and virtually all head and neck pathology (eg, parotid tumors, pathologic cervical adenopathy). There were several cases flagged for innocuous findings (eg, cerebellar vermis cyst) and normal variant anatomy (eg, mega cisterna magna) that contained additional

**Table 2: Comparison between concerns of nonradiologists about initial imaging versus impressions of neuroradiologists**

<table>
<thead>
<tr>
<th>Nonradiologist concern present</th>
<th>Incidental Finding Present</th>
<th>Incidental Finding Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonradiologist concern absent</td>
<td>52 (TP)</td>
<td>81 (FP)</td>
</tr>
<tr>
<td></td>
<td>2807 (FN)</td>
<td>13,593 (TN)</td>
</tr>
</tbody>
</table>

Sensitivity = 0.02, Specificity = 0.99

Note: TP indicates true-positive, FP, false-positive; TN, true-negative; FN, false-negative.

PPV = TP/(TP + FP), NPV = TN/(FN + TN); Sensitivity = TP/(TP + FN); Specificity = TN/(TN + FP).
undetected abnormalities (eg, ICA aneurysm). These results are expected on the basis of training and experience and particularly because the neuroradiologists’ interpretations were considered ground truth. Ultimately, the results offer insight into the prevalence and characteristics of significant lesions that would be potentially missed by using a flag and refer screening approach alone.

In the United Kingdom Biobank study, a large-scale, multimodal (abdominal, cardiac, and brain MRI) population-based cohort study of adults 40–69 years of age examining incidental findings, radiographers were trained and tasked with identifying “incidental findings that might be clinically serious or life-threatening” for referral to a specialist radiologist to review. The workflow for detection of incidental findings was examined by comparing study findings with those in the systematic radiologist review of the first 1000 imaged participants. This study found that radiographers flagged 179/1000 (18%) scans for further review by a radiologist. Radiographers detected fewer overall incidental findings than the radiologists performing systematic review (18/1000, 1.8%, versus 179/1000, 17.9%, respectively) but a relatively greater percentage with serious final diagnoses (5/18, 28%, versus 21/179, 12%). Radiographers also missed 16/21 serious final diagnoses (false-negatives), whereas a systematic radiologist review led to many final diagnoses of doubtful clinical significance (158/179, false-positives).

There are 3 crucial caveats when comparing the United Kingdom Biobank study with our study. First, only the first 1000 participants’ scans were systematically reviewed by radiologists and compared with radiographer impressions, whereas nonradiologist reviewers in our study had the opportunity to flag every scan and a neuroradiologist reviewed every scan regardless of whether it was flagged. Second, the multimodal nature of the United Kingdom Biobank study enables comparison of the abnormality detection rate for incidental findings throughout the body, whereas our study focused solely on those detectable by brain MRI. Last, our research protocols prevent verification of final diagnoses via supplemental diagnostic studies. When comparing studies, nonradiologist reviewers in the United Kingdom Biobank study flagged scans at greater rates (179/1000, 17.9%) versus our study (33/16,400, <1%). They also flagged scans in which abnormalities were detected and confirmed by radiologists at similar rates (21/179, 12%, versus 22/133, 16%). Overall, both studies demonstrated that nonradiologists flagged few scans with potentially serious abnormalities.

Our study has several limitations. First, we could not verify provisional neuroradiologic diagnoses on the basis of research brain scans, but these were, nonetheless, considered the ground truth. This issue is because subsequent clinical evaluations prompted by incidental findings were separate institutional review board–approved study activities and the anonymized research protocol forbade follow-up communication with participants receiving follow-up. Second, some participants were scanned more than once, potentially leading to overrepresentation of findings in any given volunteer. However, the authors estimated that fewer than 2000 participants were serially scanned. In the context of 16,400 volunteers, it is unlikely that serially scanned participants had a statistically significant impact on summary results, and some serial scans revealed new significant findings, justifying independent analysis of all scans. Third, research brain MRIs are not performed for diagnostic purposes. Although acquired on high-quality MR imaging scanners and interpreted by neuroradiologists, research brain MRIs contain only the sequences necessary to suit the purpose of each study. Therefore, it is likely that some clinically significant brain abnormalities went undetected due to limited research imaging protocols.

Few protocols included MRA, resulting in a lower-than-expected detection rate for aneurysms in this large population. Conversely, “soft calls,” or provisional diagnoses based on limited information and/or with low confidence were more likely to occur out of caution on the part of the neuroradiologist interpreting each scan. Last, our discovery that nonradiologists showed very low sensitivity to abnormalities compared with neuroradiologists may be biased because nonradiologists knew that every scan underwent expert review. Accordingly, initial appraisals of scans by nonradiologists may have been more cursory and thus less sensitive compared with a scenario in which scans are expertly interpreted only on request. We emphasize that the comparison of nonradiologists with neuroradiologists was performed not to compare diagnostic performance per se but to help quantify the effect on discovery of significant lesions using either approach.

CONCLUSIONS

Incidental findings are previously unknown lesions of potential clinical significance found in brain MRIs performed for research volunteers. In a large series of research volunteers, incidental findings were found in roughly 4% of brain MRIs. The most common type of incidental finding was vascular disease followed by neoplastic and congenital lesions. When asked to note any concerning lesions on the initial image acquisition, scanning staff and research personnel flagged <2% of scans later found to contain at least 1 significant finding by neuroradiologists. Given the frequency of clinically relevant abnormalities coupled with a low abnormality detection rate by nonradiologists, routine neuroradiologist review of all research brain MRI scans should be considered to ensure that potentially serious abnormalities are detected.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.
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ABSTRACT

BACKGROUND AND PURPOSE: Superagers are defined as older adults with episodic memory performance similar or superior to that in middle-aged adults. This study aimed to investigate the key differences in discriminative networks and their main nodes between superagers and cognitively average elderly controls. In addition, we sought to explore differences in sensitivity in detecting these functional activities across the networks at 3T and 7T MR imaging fields.

MATERIALS AND METHODS: Fifty-five subjects 80 years of age or older were screened using a detailed neuropsychological protocol, and 31 participants, comprising 14 superagers and 17 cognitively average elderly controls, were included for analysis. Participants underwent resting-state-fMRI at 3T and 7T MR imaging. A prediction classification algorithm using a penalized regression model on the measurements of the network was used to calculate the probabilities of a healthy older adult being a superager. Additionally, ORs quantified the influence of each node across preselected networks.

RESULTS: The key networks that differentiated superagers and elderly controls were the default mode, salience, and language networks. The most discriminative nodes (ORs > 1) in superagers encompassed areas in the precuneus posterior cingulate cortex, prefrontal cortex, temporoparietal junction, temporal pole, extrastriate superior cortex, and insula. The prediction classification model for being a superager showed better performance using the 7T compared with 3T resting-state-fMRI data set.

CONCLUSIONS: Our findings suggest that the functional connectivity in the default mode, salience, and language networks can provide potential imaging biomarkers for predicting superagers. The 7T field holds promise for the most appropriate study setting to accurately detect the functional connectivity patterns in superagers.

ABBREVIATIONS: ASSET = array spatial sensitivity encoding technique; BOLD = blood oxygen level-dependent; DMN = default mode network; ECN-L = executive control network left; ECN-R = executive control network right; EN = elastic net; ICA = independent component analysis; IPAT = integrated parallel acquisition technique; rs-fMRI = resting-state fMRI; OLS = ordinary least squares; SN = salience network

Aging is an increasingly global phenomenon, usually accompanied by cognitive decline, with direct implications for the health care system and individuals’ lives.1 In this setting, subjects with superior memory performance in late life (80 years of age or older) stand out because they have a model capable of clarifying the brain mechanisms underlying cognitive resilience. These subjects have been identified as “superagers” in the literature.3-5 To date, it is known that superagers show selective cortical preservation in particular regions of the default mode network (DMN) and salience network (SN), overlapped by stronger functional connectivity, highlighting possible key hubs for memory and cognition.3-5 However, these studies included subjects from 60 years of age, which may be biased to obtain meaningful assertions about “youthful” memory performance in late life (80 years of age and older).6

Cognitive maintenance in older adults may reflect intrinsic functional integrity as a neurobiologic substrate.7 fMRI can play an important role in detecting key brain hubs sustaining youthful cognition, thereby contributing to understanding the most resilient brain areas in superagers. Moreover, alterations in the brain functional connectome were previously reported to provide biomarkers for age-related cognitive decline and Alzheimer disease.8
Resting-state fMRI (rs-fMRI) focuses on the temporal characteristics and spatial organization of spontaneous fluctuations of the blood oxygen level–dependent (BOLD) signal and is powerful for characterizing brain organization and its abnormalities. Because the discrepancies between superagers and cognitively average elderly controls may be modest but important to detect early changes in brain function, using an ultra-high-field rs-fMRI with increased spatial and temporal resolution may allow study of more subtle disruption.9 This is the first time that older adults with superior memory performance have been investigated at a 7T field.

In this study, we compared the differences in the resting-state functional connectivity between superagers and cognitively average elderly controls (elderly controls) in a range of neural networks with the aim of identifying the most discriminative networks and within-network nodes for predicting superagers. We additionally examined differences in the prediction probability of being a superager between the rs-fMRI data at 3T and 7T magnetic fields. We hypothesized that hub regions are critical to predicting youthful cognitive function in superagers, and the measurements of functional connectivity would be improved at a higher magnetic field.

MATERIALS AND METHODS

Selection of Participants
Initially, 55 participants were recruited from different centers in the city of Sao Paulo, Brazil, as detailed previously by de Godoy et al.10 and the neuropsychological tests were performed at the Department of Neurology of Hospital das Clinicas (Medical School of the University of Sao Paulo). Informed consent was obtained from each participant and the research project was approved by the Ethics Committee of the University of Sao Paulo (#62047616.0.0000.0068). The study was designed and conducted according to the Declaration of Helsinki.

The inclusion criteria for the participants were the following: 1) 80 years of age and older; 2) education of ≥ 4 years; 3) Mini-Mental State Examination scores normal for the individuals’ education;11,12 4) Functional Activity Questionnaire score of ≤ 4;13 5) Clinical Dementia Rating score equal to zero; and 6) a result of the 15-question version of the Geriatric Depression Scale of ≤ 5.

The exclusion criteria included the following: 1) a diagnosis of dementia or mild cognitive impairment according to the National Institute on Aging and Alzheimer’s Association criteria;14,15 2) a diagnosis of a major psychiatric disorder by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; 3) a history of alcohol or psychoactive drug abuse; 4) current or previous diagnosis of diseases of the CNS (ie, stroke or seizure); 5) the presence of structural lesions in the CNS on imaging that could distort the brain parenchyma (ie, tumor or brain malformation); and 6) visual and/or auditory limitations that impair the performance of cognitive tests.

The flow charts of participant selection and the neuropsychological tests performed are shown in Fig 1 and the Online Supplemental Data, respectively.

Neurocognitive Screening
The first assessment consisted of a semistructured interview with the collection of sociodemographic data; cognitive assessment using the Mini-Mental State Examination, Montreal Cognitive Assessment, and the Brief Cognitive Screening Battery;16 screening for depressive symptoms and anxiety using the Geriatric Depression Scale-15 and the Geriatric Anxiety Inventory, respectively; and functional assessment with the Functional Activity Questionnaire and Clinical Dementia Rating.

Subsequently, the subjects who met the inclusion criteria underwent neuropsychological tests. The tests included the Forward and Backward Digit Span, Trail-Making A and B, Verbal Fluency (animals) and Letter Verbal Fluency tests, Rey-Osterrieth Complex Figure (copy and delayed recall), Logical Memory of the Wechsler Memory Scale, Rey Auditory Verbal Learning Test, 60-item version of the Boston Naming Test, and Estimated Intelligence Quotient measured with the Wechsler Adult Intelligence Scale, Third Edition. Those who performed equal or less than −1.5 SDs from average normative values adjusted by age and education for any cognitive test aforementioned were excluded.

Healthy Older Adult Grouping
Participants were separated into 2 groups: superagers (n = 14; mean age, 82.93 [SD, 3.47] years) and cognitively average elderly controls (n = 17; mean age, 84.47 [SD, 4.29] years). Superagers were defined as the participants who presented with a delayed recall score (30 minutes) in the Rey Auditory Verbal Learning Test, used as a measure of episodic memory, equal to or greater than average normative values for individuals 50–60 years of age (≥9 words), according to the criteria established by the Northwestern SuperAging research program.2 In addition, to conform with these criteria, they had to perform at or above 1 SD of the average for their age and demographics for cognitive function in the nonmemory domains tests, including Forward and Backward Digit Span, 60-item version of the Boston Naming Test, Trail-Making A, Trail-Making B, Rey-Osterrieth Complex Figure, and Verbal Fluency (animals) and Letter Verbal Fluency tests.17,18 The cognitively average elderly controls performed in memory and nonmemory domains within 1 SD of the average range for their age and demographics, which means that they were average-performing older adults according to their cognitive status.

Imaging Data Acquisition
We acquired MR imaging data of 31 participants (14 superagers and 17 elderly controls) on a 3T scanner, whereas 21 of them (12 superagers and 9 elderly controls) were also imaged on a 7T scanner. The fewer subjects scanned at the 7T field were due to MR imaging safety concerns (eg, the presence of ferromagnetic aneurysm clips, pacemakers, and stents)19 and the safety measures in place during the coronavirus disease 2019 (COVID-19) pandemic.

The 3T MR imaging session was scheduled <1 month after the clinical and neuropsychological assessments. We used a Signa PET/MR imaging 3T scanner (GE Healthcare) with a 32-channel head coil. An anatomic whole-brain 3D T1-weighted scan was acquired with the parameters as follows: TR = 8 ms, TE = 3.2 ms, flip angle = 80°, array spatial sensitivity encoding technique (ASSET) factor = 1.5, FOV = 240 × 240 × 240, matrix = 240 × 240, and 180 slices of 1 mm each yielding a voxel size = 1 × 1 × 1 mm during 5 minutes 16 seconds. rs-fMRI was acquired with a T2*
weighted echo-planar imaging sequence with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 240 × 240, matrix = 80 × 80, section thickness = 3.6 mm (voxel size = 3 × 3 × 3.6 mm), number of slices = 36, gap = 0.4 mm, ASSET factor = 2.5. Although 208 volumes were acquired during 6 minutes 56 seconds, the first 4 volumes were discarded, so we had 204 volumes per subject.

The 7T MR imaging was performed after acquiring all the data on the 3T scanner and within 6 months after the clinical evaluation. We used a Magnetom 7T scanner (Siemens) with a 32-channel coil (Nova Medical). The 3D T1 image was acquired by the MP2RAGE technique with the following parameters: TR = 6000 ms, TE = 2.25 ms, flip angle = 4°/5°, TI = 800/2700 ms, integrated parallel acquisition technique (IPAT) = 3, FOV = 240 × 240, matrix = 320 × 320, and 256 slices, yielding an isotropic voxel size of 0.75 mm³ during 9 minutes 36 seconds. rs-fMRI was acquired with a T2*-weighted EPI multiband sequence, provided by the Center for Magnetic Resonance Research, with the following parameters: TR = 1500 ms, TE = 24 ms, flip angle = 70°, FOV = 210 × 210, matrix = 120 × 120, section thickness = 1.75 mm (isotropic voxel size = 1.75 mm³), number of slices = 81, no gap, multiband accel factor = 3, IPAT = 2, and 250 volumes were acquired in 6 minutes 38 seconds.

During the rs-fMRI at 3T and 7T, participants were told to keep their eyes open while looking at a fixation cross. No cognitive tasks or tests were administered before the MR imaging session.

**Brain Connectivity Analysis**

**rs-fMRI Preprocessing.** The MR imaging DICOM files were entered into an automatic pipeline in GraphiCA (https://www.brainet.ca/) (Online Supplemental Data). Anatomic and functional images were kept in native space and preprocessed using FSL 6.03 (http://www.fmrib.ox.ac.uk/fsl). Preprocessing steps of the T1-weighted anatomic images included bias field correction, brain extraction, tissue-type segmentation (CSF, gray matter, white matter), and subcortical segmentation. On the functional data, we performed skull stripping, motion correction, section-timing correction, spatial smoothing (ceiling of 1.5 × voxel size), independent component analysis (ICA)-based Automatic Removal Of Motion Artifacts, high-pass filtering of 100 seconds, and nuisance regression of white matter and CSF.

**Extraction of the Functional Networks.** Graphica performs ICA with dual regression implemented in FSL. As a part of this process, a set of independent component maps were identified for each network, and dual regression was implemented to identify subject-specific spatial maps using 11 resting-state network masks: auditory, DMN, executive control network left (ECN-L), executive control network right (ECN-R), hippocampal, language, SN, sensorimotor, visual lateral, visual medial, and visual occipital.

**Regional Parcellation.** Each subject’s T1-weighted image was automatically segmented with a pipeline implemented in FreeSurfer (Version 7.1.0; http://surfer.nmr.mgh.harvard.edu). Further parcellation was performed with Graphica using a gradient-weighted Markov Random Field Model procedure described in Schaefer et al. The procedure yielded 832 parcellated brain regions, which were included as network nodes for further analyses.

**Functional Network Construction and Thresholding.** After we coregistered each of the functional resting-state networks to the subject, a mean z value was calculated by averaging the scalar map values of the voxel belonging to each one of the 832 ROIs. The resulting z-standardized correlation coefficients describe the loading of each nodal time course on the respective resting-state networks. To remove spurious or weak z values, for instance, due to noise, the loadings were thresholded with a data-driven mixture modeling approach at a single-subject level.
Global Properties. Global properties include the number of found, missing, and extra regions. These properties were calculated on the basis of template masks created and separated by sex for each one of the functional networks using healthy controls to create a baseline for the quality index and to exclude or keep the subjects on the basis of their motion. The data from healthy controls came from the Human Connectome Project and Openneuro, comprising 319 female subjects (mean age, 22.18 [SD, 25.19] years) and 482 male subjects (mean age, 25.05 [SD, 28.26] years). The number of found regions was defined as the regions with z values different from zero that survived the thresholding process. Missing regions were defined as the regions that have not been identified but do belong to the specific functional template mask. The number of extra regions was defined as regions that do not belong to the respective functional network template mask but were found.

Regions (Belong Template Mask) = Regions (Found) + Regions (Missing) − Regions (Extra).

Statistical Analysis

Classification Analysis. The whole-brain connectivity parcellation comprises 832 ROIs. To avoid overfitting in the regression model, we selected 6 key networks for successful aging, encompassing 397 distinct ROIs, with some ROIs overlapping the networks, including the DMN, SN, ECN-L, ECN-R, hippocampal, and language networks. Penalized regression analysis used these networks and within-network nodes to determine brain regions with statistical differences between superagers and cognitively average elderly controls.

Each of the ROIs, grouped within the specific 6 networks, was considered as a covariate in the penalized regression modeling in the following way: For a set of predictors $X = X_1, \ldots, X_N$ with $p$ measurements taken on each, and the response variable $y$, regression analysis estimated the coefficients $\beta_i$ in the following linear regression model:

$$y = x_1\beta_1 + \cdots + x_N\beta_N = X\beta.$$

The ordinary least squares (OLS) regression finds a set of $\beta_i$ that minimize the sum-squared approximation error $(y - x\beta)^2$. However, in general, OLS solutions are often unsatisfactory because there is not a unique solution when $p \gg n$, and it is difficult to pinpoint which predictors are most relevant to the response. Various regularization approaches have been proposed in order to handle "large- $p$, small- $n$" data sets and to avoid overfitting, such as LASSO (Least Absolute Shrinkage and Selection Operator) and ridge regression, or a combination of both. Elastic Net (EN) addresses these shortcomings since variable selection is embedded into their model-fitting process. These methods were previously applied to a similar problem, with results suggesting that the EN regression was a more robust approach to extreme correlations among the predictors. Briefly, sparse regularization methods include the L1-norm regularization on the coefficients, which is known to produce sparse solutions, i.e., solutions with many zeros, thus eliminating predictors that are not essential.

For the analysis here, we used the EN regression that finds an optimal solution to the OLS problem objective, augmented with additional regularization terms that include the sparsity-enforcing. Specifically, there are 2 types of regularizations that EN allows: L1-norm constraint on the regression coefficients that penalizes the absolute size and "shrinks" some coefficients to zero, and a "grouping" L2-norm constraint, which penalizes the squared size of the coefficients and enforces similar coefficients on predictors that are highly correlated with each other, which L1-constraint alone does not provide. Formally, EN regression optimizes the following function,

$$L(\lambda_1, \lambda_2; \beta) = (y - x\beta)^2 + \lambda_1\|\beta\|_1 + \lambda_2\|\beta\|_2,$$

where $\lambda_1$ is the L1-penalty term and $\lambda_2$ is the quadratic penalty term.

In our case, for each of the networks, we let $y$ be a binary outcome of either being a superager or an elderly control and $X$ consisted of 397 covariate measurements representing the regions (nodes) across the 6 neural networks. We modeled the relationship as,

$$\logit(p_i) = X_i\beta_i, \quad i = 1, 2, \ldots, n.$$  

Model Prediction and Classification. Using these models, we calculated the expected probabilities of an individual being a superager predicted from the penalized regression model using the measurements of the network and plotted this as an outcome (on the y-axis) versus the binary observed values of the individual being either an elderly control or superager to evaluate the prediction performance of the model (Fig 2). The diagonal lines in Fig 2 represent the mean difference between predicted probabilities for superagers and elderly controls. The prediction model can be thought of as an OLS linear regression,

$$p_{\text{control}} + (p_{\text{superager}} - p_{\text{control}})^s,$$

where $s$ is the observed data superager indicator variable, $p_{\text{superager}}$ is the mean predicted probability of being a superager for the observed group (either control or superager), and $p_{\text{superager}} - p_{\text{control}}$ is the slope of the line, which indicates the discriminatory ability of the model. Larger values demonstrate better performance (steeper lines), and zero corresponds to no predictive ability with a horizontal line for that network.

Quantification of Regression Analysis Results. We used the regression models in Equation $\logit(p_i) = X_i\beta_i, \quad i = 1, 2, \ldots, n$ to infer the ORs describing the difference between the odds of exposure in each network and region (node) among superagers and elderly controls. In our study, they can be interpreted as a measure of the relative influence of a network and region within the likelihood of being a superager. We obtained the ORs using the fitted models to give an average comparison between individuals with or without a unit increase in a particular region $j$; if $p$ is the probability of being a superager then,

$$OR_j = \frac{p_j/(1-p_j)}{p/(1-p)} = \exp(\beta_j).$$

We used the ORs to quantify the influence of each region within each of the 6 networks. We identified the regions with the
ORs that are $>1$ to be the regions that are most differentiable/discriminative between superagers and elderly controls. If the OR values were equal to 1 (OR = 1), there was no discrimination in the examined regions between groups. Finally, if the OR values were $<1$, the regions negatively discriminated the examined region as characteristic for a superager. We noted that the $P$ value was not generated from this analysis but the significance of the influence from a network/region could be inferred from the 95% CI for an OR.27

Because the number of variables in the model was very large, the maximum number of nonzero variables was limited to 10. For the analyses, we used the statistical programming language R (https://cran.r-project.org/web/packages/glmnet) and the package glmnet.26

RESULTS

Demographics and Neuropsychological Performance Scores

Superagers and elderly controls did not differ in terms of age ($P = .304$), education ($P = .299$), or sex distribution ($P = .224$). Superagers had statistically significantly better performance compared with elderly controls in the Montreal Cognitive Assessment ($P = .003$) and some episodic memory tests, including the Delayed-Recall Brief Cognitive Screening Battery ($P = .036$), Delayed-Recall Rey Auditory Verbal Learning Test ($P < .001$), and Logical Memory Delayed-Recall ($P = .01$) (Online Supplemental Data).

Discriminative Networks and Brain Nodes for Predicting Superagers

The lollipop plots (as an alternative to bar charts) in Fig 3 show the magnitude (dot) and the range (line) of the nodes within each network that are discriminative between superagers and elderly controls. Here ORs $>1$ suggest nodes that are more likely to be different in superagers (ie, larger influence on the predicted probability of being a superager) and are illustrated by lollipops in green. Conversely, nodes with ORs $<1$ are less likely to be different in superagers (ie, these regions are negatively discriminated as a characteristic of a superager) and are illustrated by lollipops in red.

When we used the 3T and 7T data sets, though all networks were overall distinct in superagers compared with elderly controls (Fig 2), some of them were more differentiable and predictive of superagers than others. For example, for the 3T data (Fig 3A), the ORs for the SN and language networks were $>1$ across some regions, with relatively good predictive performance (Fig 2), suggesting that these regions were discriminative in superagers. In contrast, the ECN-L presented only a few regions of ORs $>1$ and others with ORs $<1$, showing a poor predictive performance. For the 7T data analysis (Fig 3B), the lollipop plots in most
networks had ORs $>1$ across several nodes and great predictive performance, characterized by a steeper slope of the diagonal lines in Fig 2. The DMN, SN, hippocampal, and language networks were the most discriminative networks in our model prediction classifier for the 7T data set. In addition, for the 7T magnetic field, we had improved sensitivity in detecting a higher number of essential regions within each network. Therefore, on the basis of the classification algorithm, when differentiating superagers from elderly controls, we were more confident using the model fit from the 7T rather than the 3T scanner.

The Online Supplemental Data delineate the anatomic space of each network studied (networks masks). Figures 4, 5, and 6 illustrate the nodes within each network in brain maps, with OR values $>1$, which predict superagers for the 3T and 7T data sets (Online Supplemental Data). We used Montreal Neurological Institute coordinates to plot the nodes and heatmaps, varying from dark blue to dark red (OR values furthest away from 1 have higher superager prediction), to demonstrate the discriminative power of each node. The Online Supplemental Data show the elastic model results for the 3T and 7T data sets for all ROIs included.

**DISCUSSION**

In this study, we identified functional networks showing that superagers exhibited distinct intrinsic connectivity compared with elderly controls in a range of brain networks and the core networks predicting a superager were the DMN, SN, and language. Areas in the precuneus posterior cingulate cortex, prefrontal cortex, temporoparietal junction, temporal pole, extrastriate superior cortex, and insula were the most discriminative nodes within these networks. By exploring the 7T and the 3T data sets separately, we could demonstrate higher prediction task confidence in rs-fMRI data sets acquired with the 7T rather than with the 3T scanner.

During the past years, clinical fMRI at 7T has gained traction because it offers a beneficial increased SNR and BOLD contrast over conventional 1.5T and 3T MR imaging scanners, translated into a greatly enhanced spatial resolution of functional activity, the main clinical advantage of 7T fMRI. A prior study demonstrated up to 300% improvement in the temporal SNR and resting-state functional connectivity coefficients provided by ultra-high-field 7T fMRI compared with 3T, indicating enhanced power for the detection of functional neural architecture. We have shown that the higher BOLD contrast-to-noise ratio available at 7T yielded improved sensitivity in detecting differences in the activity across all networks compared with the 3T field, reflected by a steeper gradient of the lines in the prediction classification algorithm. Moreover, higher ORs (OR $>1$) were observed across several nodes for the 7T compared with the 3T data set. These differences imply that 7T scanners may facilitate
high-quality connectivity measurements capturing stronger evoked rs-fMRI responses, hence offering potentially greater group-level power. This possibility raises our confidence for the results of the within-network nodes and overall model fit from the 7T scanner. Therefore, in the discussion below, the discriminatory nodes for identifying superagers at the 7T data set are emphasized more.

In line with previous studies including successful agers from 60 years of age, we have found important features for predicting superagers in the DMN and SN. The DMN is implicated in memory encoding, storage, and retrieval, while the SN is believed to be associated with executive processes and detecting emotionally relevant stimuli, as well as alerting. In parallel, normal aging is associated with decreased signal complexity within the DMN and SN nodes, and there is a disrupted variability in these networks in mild cognitive impairment and Alzheimer disease. It stands to reason that the DMN and SN hubs may potentially provide valid and reliable biomarkers for early age-related cognitive decline.

Beyond the classic hubs of the DMN and SN, we also found discriminative nodes within the ECN-L/R, language, and hippocampal networks for predicting a superager among elderly controls. The ECN is generally involved in tasks relying on executive functions, such as the control process and working memory. The hippocampal network plays an important role in the consolidation of short-term memory and spatial memory. The language network, a critical connectome in our model, encompasses regions of the Broca (inferior frontal) and Wernicke (superior temporal with extension into the inferior parietal cortex) areas and has not been previously investigated in understanding the superior preservation of cognitive abilities. Although our groups did not show significant differences in verbal fluency tests, modifications in the language functional connectivity may anticipate changes in language performance in healthy older adults. Moreover, it is well-known that the language network can accurately discriminate patients with mild cognitive impairment from healthy controls and is also known to demonstrate weaker functional connectivity in Alzheimer disease.

The nodes with superior importance for predicting superagers encompassed areas in the extrastriate superior cortex, precuneus posterior cingulate cortex in both hemispheres; inferior parietal lobule, the temporoparietal junction, intraparietal sulcus, insula, and medial temporal pole in the right brain hemisphere; and the prefrontal/dorsal prefrontal cortex, temporo-occipital junction, and retrosplenial cortex in the left hemisphere. Most interesting, most of these cortical nodes presented with stronger intrinsic functional connectivity and volumetric preservation akin to features of younger adults in previous studies. These nodes also have been considered as key brain functional hubs for diverse cognitive functions and information integration among segregated functional networks.

Our results indicate that the posterior cingulate cortex, a region mainly engaged in episodic memory, plays a crucial role. Our previous study on superagers showed a higher total NAA concentration in superagers than in elderly controls in the posterior cingulate cortex, reflecting a metabolically active brain region contributing to superior cognition in late life. Therefore, the functional and metabolic features of this structure observed in our cohort may underlie the superagers’ significantly higher scores in the episodic memory tests. The prefrontal cortex, one of the most discriminative nodes in our cohort, is known to be associated with executive functions (planning, decision-making) and...
social-cognitive processes. Another powerful discriminatory node, the right temporoparietal junction, is engaged in the social domain (empathy, sympathy) and self-evaluating behavior. It was previously observed that superagers present with an increased level of positive relations with others, defined by truthfulness and satisfaction, and they manage stress better.

Among the discriminative nodes from the classifier, the inferior parietal cortex is known to be involved in semantic processing and attention. The insula contributes to various brain functions through the integration of sensory, emotional, and cognitive information. Moreover, the extrastriate superior cortex, involved in visual-processing information, plays an important role in the DMN and hippocampal networks. These nodes highlight how structures not directly involved with memory can contribute to superior memory performance.

Our study has a number of limitations. Our cohort was small due to the constraints in data collection and for prioritizing a rigorous selection protocol, preventing splitting the data set into training and validation samples. Also, the individuals scanned at 7T were a subset of those scanned at 3T due to patient contraindication heightened at 7T. Because for each individual, there were hundreds of measurements introducing a risk of overfitting, the penalized regression methodology was selected. The results should be seen as a contribution to the field and not definitive, because we aimed to investigate the signal that can be found in the data set in the presence of a low number of subjects and possible measurement error. The regression method used did not generate significant P values; however, even if we used standardized methodologies, these would have to be caveated. Moreover, we compared superagers with cognitively healthy older adults, reflecting early and subtle age-related cognitive functional changes; therefore, remarkable differences would not be expected.

The increased spatial resolution of BOLD on 7T and secondary higher detection of intrasubject variability can overestimate the intragroup differences in a small sample size. There are also problems concerning B0 and B1 inhomogeneity created by higher field strengths, resulting in geometric distortion and drop-out, respectively, demanding advanced shimming and specialized pulse sequence designs. The shorter TE (7T: 24 ms versus 3T: 30 ms), thinner slices (7T: 1.75 mm versus 3T: 3.6 mm), and parallel imaging can avoid some of these issues by reducing intravoxel inhomogeneity and through-plane dephasing. The present study also had constraints regarding differences in acquisition protocols between the 3T and 7T scanners. First, the voxel size was different in 7T (isotropic voxel size = 1.75 mm3) compared with 3T (voxel size = 3 × 3 × 3.6 mm). The precision of the whole-brain functional connectivity maps shown in this study may have been impacted by the smaller voxel size of the 7T protocol compared with 3T. The TR was also longer at 3T (TR = 2000 ms) compared with 7T (TR = 1500 ms), indicating that the number of frames was higher for 7T for the same scan time. The higher number of frames is expected to improve the temporal resolution of the 7T scan compared with 3T. Ultimately, the acceleration factor was higher at 7T (multiband acceleration factor 3, IPAT 2) compared with 3T (ASSET factor 2.5), which can reduce signal distortion, signal drop-out, and partial volume effects but can also increase motion sensitivity and reduce the SNR. Even though we highlight advancements in numerous metrics, including temporal SNR, sensitivity to detect connectivity measurements, and whole-brain connectivity maps for the data set at 7T compared with 3T, some results may be affected by differences in acquisition protocols and different scanners.

**FIG 5.** The most discriminative nodes among the ECN-L and ECN-R in superagers compared with elderly controls. The heatmap varies from dark blue to dark red (denoting a higher prediction rate for classification as a superager using ORs). RH indicates right hemisphere; LH, left hemisphere; L, left; R, right.
CONCLUSIONS

Our findings indicated that rs-fMRI may be a useful technique in assessing youthful memory performance in late life and identifying potential superagers, particularly in nodes among the DMN, SN, and language network. Our results highlight the benefit of 7T over the 3T magnetic field scanners for this diagnostic and classification task and warrant further validation in larger prospective studies.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES


FIG 6. The most discriminative nodes among the hippocampal and language networks in superagers compared with elderly controls. The heat-map varies from dark blue to dark red (denoting a higher prediction rate for classification as a superager using ORs). RH indicates right hemisphere; LH, left hemisphere; L, left; R, right.
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Infarct Evolution in Patients with Anterior Circulation Large-Vessel Occlusion Randomized to IV Alteplase and Endovascular Treatment versus Endovascular Treatment Alone


ABSTRACT

BACKGROUND AND PURPOSE: Infarct evolution after endovascular treatment varies widely among patients with stroke and may be affected by baseline characteristics and procedural outcomes. Moreover, IV alteplase and endovascular treatment may influence the relationship of these factors to infarct evolution. We aimed to assess whether the infarct evolution between baseline and follow-up imaging was different for patients who received IVT and EVT versus EVT alone.

MATERIALS AND METHODS: We included patients from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)-NO IV trial with baseline CTP and follow-up imaging. Follow-up infarct volume was segmented on 24-hour or 1-week follow-up DWI or NCCT. Infarct evolution was defined as the follow-up lesion volume: CTP core volume. Substantial infarct growth was defined as an increase in follow-up infarct volume of >10 mL. We assessed whether infarct evolution was different for patients with IV alteplase and endovascular treatment versus endovascular treatment alone and evaluated the association of baseline characteristics and procedural outcomes with infarct evolution using multivariable regression.

RESULTS: From 228 patients with CTP results available, 145 patients had follow-up imaging and were included in our analysis. For patients with IV alteplase and endovascular treatment versus endovascular treatment alone, the baseline median CTP core volume was 17 (interquartile range = 4–35) mL versus 11 (interquartile range = 6–24) mL. The median follow-up infarct volume was 13 (interquartile range, 4–48) mL versus 17 (interquartile range = 4–50) mL. Collateral status and occlusion location were negatively associated with substantial infarct growth in patients with and without IV alteplase before endovascular treatment.

CONCLUSIONS: No statistically significant difference in infarct evolution was found in directly admitted patients who received IV alteplase and endovascular treatment within 4.5 hours of symptom onset versus patients who underwent endovascular treatment alone. Collateral status and occlusion location may be useful predictors of infarct evolution prognosis in patients eligible for IV alteplase who underwent endovascular treatment.

ABBREVIATIONS: EVT = endovascular treatment; eTICI = expanded treatment in cerebral ischemia; FIV = follow-up infarct volume; IQR = interquartile range; IVT = IV alteplase; mAOL = modified arterial occlusive lesion; RCT = randomized controlled trial

Endovascular treatment (EVT) preceded by administering IV alteplase (IVT) is the current standard of care and is effective in patients with acute ischemic stroke.1 A first meta-analysis of 3 Asian randomized controlled trials (RCTs) comparing EVT alone with IVT before EVT suggested non-inferiority of EVT alone.2 However, 4 following RCTs, including...
In this post hoc analysis of the MR CLEAN-NO IV trial, we aimed to assess whether the infarct evolution between baseline and follow-up imaging was different for patients who received IVT and EVT versus EVT alone. Additionally, we aimed to identify which clinical and procedural outcomes are associated with infarct evolution in patients with acute ischemic stroke who received IVT and EVT versus EVT alone.

**MATERIALS AND METHODS**

**Patient Selection**

We included patients with baseline CTP and follow-up DWI or NCCT from the MR CLEAN-NO IV trial. The MR CLEAN-NO IV trial included patients with acute ischemic stroke due to an intracranial proximal occlusion of the anterior circulation who were directly admitted to an EVT-capable center between January 2018 and October 2020. If eligible for EVT and IVT administration within 4.5 hours, patients were randomly assigned to receive either EVT alone or IVT followed by EVT. Analyses were performed in the as-treated population. Details of the trial protocol were previously published. A flow chart explaining the inclusion criteria of this study is provided in Fig 1.

**Image Acquisition and Postprocessing**

Baseline CTP images were acquired according to site-specific baseline CT acquisition protocols. CTP data were centrally postprocessed by an independent core lab using syngo.via (Version VB40; Siemens). The ischemic core was estimated using a CBV of <1.2/100 mL, and the penumbra was estimated using a CBF of <27/100 mL/min. A smoothing filter (smoothing strength, 10 mm) was applied. Expert visual-quality assessment of the CTP results was performed by 2 experienced neuroradiologists (with >10 and >15 years of experience), and cranio-caudal cropping was allowed to remove obvious artifacts at the level of the skull base. Follow-up imaging was acquired at a median of 24- to 48-hour DWI, 24-hour NCCT, or 5- to 7-day NCCT. DWI was the preferred technique for determining the follow-up infarct volume (FIV). If DWI was not available, follow-up NCCT was used to segment the FIV using a semiautomated segmentation method, with subsequent expert visual-quality assessment (>15 years of experience). In case both 24-hour and 5- to 7-day NCCT were available, the 5- to 7-day NCCT was used to assess the FIV. If hemorrhagic transformation was present, the hemorrhagic regions were included in the segmentation volume. Hemorrhagic transformation was scored by an independent core lab and defined according to the Heidelberg Bleeding Classification. Recanalization on follow-up imaging was assessed on either CTA or MRA using the modified arterial occlusive lesion (mAOL) score.

**Infarct Evolution and Imaging Assessment**

We compared the infarct evolution and occurrence of substantial lesion growth between patients who received IVT and EVT versus patients who underwent EVT alone. Infarct evolution was calculated by subtracting the CTP core volume from the FIV. Overestimation of the FIV by CTP was defined as CTP core volume of >FIV. Substantial infarct growth was defined as an increase in FIV of >10 mL. All imaging data were assessed by an independent core laboratory of neuroradiologists or radiologists. Postprocedural reperfusion was assessed on postprocedural DSA. Successful reperfusion was defined as extended TICI (eTICI) 2b–3, and complete reperfusion was defined as eTICI 3. Recanalization
large hemorrhages between baseline and follow-up imaging can strongly affect the FIV assessment. Both sensitivity analyses are reported in the Online Supplemental Data.

**Protocol Approval and Patient Consent**

The MR CLEAN-NO IV trial protocol was approved by national central ethics committees and by research boards at each participating center. The final versions of the trial protocol and statistical analysis plan are both available at www.nejm.org. The MR CLEAN-NO IV trial was conducted in accordance with the revised Helsinki guidelines.

**Data Availability**

Individual patient data cannot be made available under Dutch law because we did not obtain patient approval for sharing individual patient data. All syntax files and output of statistical analyses are available on reasonable request.

**RESULTS**

From 539 patients included in the MR CLEAN-NO IV trial, 228 had available CTP results. Of these 228 patients, follow-up imaging was performed in 145 patients, and they were included in our post hoc analysis. Eighty-one (56%) patients received IVT and EVT. Baseline characteristics such as age, sex, and baseline NIHSS were comparable for patients who received IVT and EVT versus patients who underwent EVT alone. Median baseline CTP-estimated ischemic core volume was 17 (interquartile range [IQR] = 4–35) mL versus 11 (IQR = 6–24) mL (P = .5). The median FIV was 13 (IQR = 4–48) mL versus 17 (IQR = 4–50) mL (P = 1.0). CTP ischemic core overestimation of >10 mL occurred in 17/81 (21%) versus 9/64 (14%) patients and occurred primarily in the white matter. The time between baseline CTP and follow-up imaging was comparable (27 versus 33 hours, P = .3). Good functional outcome occurred in 45/81 (56%) patients who received IVT and EVT versus in 37/64 (58%) patients who received EVT alone (OR = 0.86; 95% CI, 0.42–1.73; P = .7). Four (3%) patients showed early recanalization (ie, recanalization before EVT). Two patients with early recanalization received IVT before EVT. An example of a patient with a left-sided M1 occlusion and a baseline CTP-estimated core of 65 mL is shown in Fig 2. This patient underwent successful EVT alone (eTICI 3) with an onset-to-reperfusion time of 195 minutes. Follow-up CTA showed a visible calcified embolus in the left M1 (mAOL 0). Follow-up DWI showed substantial infarct growth (384 mL). See the Online Supplemental Data for a complete description of baseline, procedural, and outcome characteristics stratified per study subgroup.

**Association of Baseline Characteristics and Procedural Outcomes with Infarct Evolution**

Univariable analyses showed that better collateral status was negatively associated with substantial infarct growth, and early
re-occlusion of the target artery at 24-hour follow-up imaging was positively associated with substantial infarct growth. In addition, the number of attempts during EVT and the occurrence of any hemorrhage were positively associated with substantial infarct growth (Online Supplemental Data). Notably, reperfusion (eTICI) was not associated with infarct evolution. The distribution of infarct evolution stratified by reperfusion subgroup is shown in Fig 3.

After adjustment for confounders, better collateral status and a more distal occlusion location were negatively associated with substantial infarct growth. The number of attempts during EVT and the occurrence of any hemorrhage were positively associated with substantial infarct growth. Early re-occlusion of the target artery was not associated with substantial infarct growth in multivariable analysis. For all included variables, the variance inflation factors were <1.5, indicating no correlation between the included independent variables (Online Supplemental Data). An exploratory analysis in a subgroup of patients without any hemorrhagic transformation (n = 103) consistently showed that better collateral status and more distal occlusion location were negatively associated with substantial infarct growth.

Infarct Evolution for Patients Who Received IVT and EVT versus EVT Alone
Substantial infarct growth (ie, infarct growth of >10 mL) occurred in 27/81 (33%) patients with IVT and EVT versus 27/64 (42%) patients who underwent EVT alone (P = .3). After adjustment for confounders, substantial infarct growth was not significantly associated with the administration of IVT and EVT (adjusted OR = 0.63; 95% CI, 0.30–1.32; P = .2). Boxplots showing the infarct growth per subgroup are provided in Fig 4.

Infarct Evolution for Patients with and without Successful Reperfusion
One hundred twelve (84%) patients achieved successful reperfusion after EVT. Patients with successful reperfusion showed lower median infarct evolution rates compared with patients without successful reperfusion (1 [IQR = 7–20] mL versus 15 [IQR = 2–71] mL), though this difference was not statistically significant (P = .2). From 59 patients with complete reperfusion (ie, eTICI 3), 20 (34%) showed substantial infarct growth.

Effect of Follow-up CTA or MRA Recanalization Status on Infarct Evolution
Follow-up CTA or MRA was available for 132 patients and showed incomplete patency of the target artery in 10% of patients receiving IVT and EVT versus in 15% of patients receiving EVT alone. However, this difference was not statistically significant (P = .3). In multivariable analysis, early re-occlusion of the target artery, assessed on follow-up CTA or MRA, was not associated with infarct growth (adjusted OR = 1.48; 95% CI, 0.28–7.83).
DISCUSSION

In this post hoc analysis of the MR CLEAN-NO IV trial, we did not observe a statistically significant difference in infarct evolution between directly admitted patients who received IVT and EVT versus patients who underwent EVT alone within 4.5 hours after symptom onset. Overall, successful reperfusion rates were similar in patients who received IVT and EVT versus EVT alone. Furthermore, our results demonstrated that collateral status, occlusion location, the number of attempts during EVT, and occurrence of any hemorrhage were statistically significantly associated with substantial infarct growth in patients who received IVT and EVT versus EVT alone within 4.5 hours after symptom onset.

Our results showed that re-occlusion on follow-up imaging was not uncommon. However, frequencies of re-occlusion were comparable between both groups. Most interesting, re-occlusion on follow-up imaging was not statistically significantly associated with substantial infarct growth after adjusting for potential confounders. However, this nonintuitive finding might be explained by the fact that our sample size was limited and, therefore, potentially underpowered to detect a clear association. The observed rates of re-occlusion on follow-up imaging are in line with a previous study assessing vessel patency at 24-hour follow-up imaging using the mAOL score. Other studies assessing re-occlusion after EVT reported rates of early re-occlusion ranging from 3% to 9%. However, these studies used different imaging techniques and grading systems to assess the vessel patency on follow-up imaging (eg, 24-hour follow-up angiography using the Qureshi grading scheme).

Our results showed that substantial infarct growth was associated with the number of attempts during EVT, which is in line with a previous large prospective study from multiple stroke registries. In addition, our results suggested that in the hyperacute (0–4.5 hour) time window, patients with poor collaterals have a higher likelihood of substantial infarct growth compared with patients with good collaterals. This finding is also in concordance with previous research in patients with stroke who underwent EVT within 6 hours of symptom onset.

If replicated, the relatively high frequency of re-occlusion within 24 hours after endovascular treatment could imply that there might be a potential added benefit of thrombolytic therapy in addition to EVT to improve functional outcome after stroke. This possibility would also be in line with the preliminary findings from the Chemical Optimization of Cerebral Embolectomy (CHOICE) trial, which showed that adjunct intra-arterial alteplase in patients with large-vessel occlusion stroke resulted in a greater likelihood of excellent neurologic outcome at 90 days. Also, the authors showed that additional intra-arterial thrombolysis was associated with an increased likelihood of achieving excellent angiographic reperfusion (ie, eTICI 2c–3). However, the proportion of patients with infarct growth between baseline and follow-up imaging was not statistically significantly different between both study groups. This result could imply that additional factors such as, for example, microvascular perfusion may also contribute to functional outcome at 90 days and that these factors might be affected by additional thrombolytic therapy in patients treated with EVT.
Several limitations to our study should be noted. First, selection bias may have been introduced because CTP was not mandatory for inclusion in the MR CLEAN-NO IV trial and CTP was performed according to local imaging protocols. Of note, not all centers routinely performed CTP in every admitted patient with suspected stroke. A total of 228 (41%) patients in the MR CLEAN-NO IV had CTP available from 17 participating centers. Of these 228 patients, 145 (64%) patients had baseline CTP with follow-up NCCT or MR imaging available, leading to a relatively small sample size. However, the baseline, imaging, and outcome characteristics of patients without follow-up imaging were comparable with those in the overall MR CLEAN-NO IV population. Second, the MR CLEAN-NO IV trial had no standardized CTP acquisition protocol, and CTP data were acquired according to local acquisition protocols per site, possibly introducing differences in CTP ischemic core volume estimations. However, all CTP data were centrally processed using a previously described single postprocessing protocol.

Furthermore, differences in CTP results that are caused by differences in acquisition protocols are commonly largely driven by differences in contrast medium injection protocols, and because the particular contrast medium injection protocols from centers in the MR CLEAN-NO IV were similar, we expect that the effect of using data from different acquisition protocols is limited. Third, FIV was measured on both 24-hour and 1-week follow-up NCCT and MR imaging. This practice could have affected the accuracy of our FIV assessments because it is known that edema affects the FIV on NCCT after stroke, and it can be challenging to distinguish edema from infarcted tissue on NCCT. However, the FIVs were not different for patients who received a median 24-hour follow-up DWI versus patients with 24-hour follow-up NCCT. In addition, it has been demonstrated that FIV assessed on 24-hour NCCT is equally strongly associated with functional outcome as the FIV measured on 1-week NCCT, regardless of the fact that infarct growth between 24-hour and 1-week imaging is common.

Fourth, hemorrhagic regions were included in the final infarct lesion, possibly affecting our results. An exploratory analysis in a subgroup of patients without any hemorrhagic transformation (n = 103) consistently showed that collateral status and occlusion location were associated with substantial infarct growth. Excluding all patients with hemorrhagic transformation from our analyses could potentially introduce bias because it is not well-known how infarct growth changes with time and what the tempo of blood-brain barrier disruption and development of hemorrhagic transformation is.

It is known that CTP may overestimate the FIV (ie, the “ghost infarct core concept”), especially in patients with successful reperfusion in the early time window. However, rates of overestimation of >10 mL were comparable with rates previously reported in a post hoc analysis of the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke (HERMES) trials collaboration.

Similarly, we found that CTP ischemic core overestimation by syngo.via predominantly occurred in the white matter. Because previous studies have shown that ischemic core thresholds might differ between gray and white matter, future studies focusing on improving white matter ischemic core estimation by syngo.via should consider this difference.

Finally, the timing of follow-up scans had a wide range (1–288 hours posttreatment). Because we showed that infarct growth was common in our population, the timing of follow-up imaging could have affected the accuracy of FIV measurements. A pooled analysis on this topic from all trials investigating the noninferiority of EVT alone is warranted for confirmation of whether infarct growth differs between patients who received IVT and EVT versus patients who underwent EVT alone. Ideally, follow-up imaging should be acquired at similar time points using a single technique.

CONCLUSIONS
No statistically significant difference in infarct evolution was found in patients who received IVT and EVT versus patients who underwent EVT alone. Collateral status, occlusion location, and number of attempts during EVT are significantly associated with substantial infarct growth in IVT-eligible patients who undergo EVT.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES


ABSTRACT

BACKGROUND AND PURPOSE: Mechanical thrombectomy appears to be a promising option for distal medium-vessel occlusions, for which intravenous thrombolysis is effective but may be insufficient when used alone. This study aimed to determine the optimal technique for these distal mechanical thrombectomies using the human placenta model.

MATERIALS AND METHODS: Twenty-four procedures were performed, allowing comparison of direct aspiration (n = 12) versus the combined technique (n = 12). Two positions of the aspiration catheter were tested for each of these techniques: in direct contact with the clot and at a distance from it [5–10 mm]. Two types of clots were tested: red blood cell–rich clots and fibrin-rich clots. First-pass recanalization and induced arterial collapse and traction were assessed.

RESULTS: The first-pass recanalization was less frequent for direct aspiration than for the combined technique, without reaching statistical significance (41.7% versus 75.0%, P = .098). Full collapse (P < .001) and extended arterial traction (P = .001) were significantly less frequent for direct aspiration. For direct aspiration with the aspiration catheter not in direct contact with the clot, there was not a single first-pass recanalization and there was systematic arterial collapse, resulting in a no-flow in the aspiration syringe.

CONCLUSIONS: The combined technique appears to be more harmful, and although direct aspiration has a lower rate of first-pass recanalization, it seems appropriate to try direct aspiration as a first-line procedure. However, if the aspiration catheter cannot reach the clot, it is not useful or even risky to try aspiration alone. These results need to be confirmed by clinical studies.

ABBREVIATIONS: ACS = arterial collapse score; ATS = arterial traction score; DA = direct aspiration; DMVO = distal medium-vessel occlusion; FPR = first-pass recanalization; HP = human placenta; MT = mechanical thrombectomy; PLVO = proximal large-vessel occlusion; RBC = red blood cell

Randomized controlled trials on acute ischemic stroke due to proximal large-vessel occlusion (PLVO) established the superiority of mechanical thrombectomy (MT) in addition to the best medical management, including IV thrombolysis, over the best medical management alone within 6 hours from symptom onset.1 More recent trials have demonstrated that the time window for MT can be extended up to 162 or 24 hours3 from the last time the patient was known well, when the selection is based on neuroimaging evaluation showing a salvageable penumbrae or a mismatch between clinical deficit and infarct size.4 Different techniques are currently used to perform these procedures, including stent retriever alone, the direct aspiration (DA) technique, and the combined techniques (ie, using different techniques such as stent retriever and an aspiration catheter at the same time). However, there is no consensus on the optimal technique for thrombectomy. Although IV thrombolysis is more effective for the small clots of distal medium-vessel occlusions (DMVOs) than for the large clots of PLVOs,4,5 IV thrombolysis alone is sometimes insufficient for DMVOs, recanalizing only one-third to one-half of the occluded vessels.6,7 With the iterative advances in device technology, MT is emerging as a promising solution for these DMVOs for several reasons.8 First, the considerable benefit of MT for PLVOs suggests that MT would also be beneficial for DMVOs; second, the advent of MT for PLVOs has led to rapid advances in catheter technology, leading to more navigable and smaller devices capable of reaching more distal and narrower vessels; third, an adverse event during MT for PLVOs is thrombus fragmentation with emboli in the distal arteries (thus, for maximum benefit from MT for PLVOs, rescue endovascular treatment of these distal
embol is desirable). Evaluation of Mechanical Thrombectomy in Acute Ischemic Stroke Related to a Distal Arterial Occlusion (DISCOUNT9) (NCT05030142) is a multicenter open, randomized controlled trial that is currently recruiting. The main objective of this trial is to assess the efficacy of MT in addition to the best medical treatment compared with the best medical treatment alone in acute ischemic stroke related to a DMVO.

The more tortuous access route and greater mobility of DMVOs, combined with thinner arterial walls, potentially increase the risk of complications, especially hemorrhages. Arterial collapse and traction induced by thrombectomy devices, particularly by avulsion of the cortical arteries or perforating branches, are phenomena thought to be responsible for these hemorrhagic complications. It is, therefore, necessary to study which techniques are the least harmful and most effective, especially between the DA technique and the combined technique, which are commonly used for this indication.

The human placenta (HP) is a validated vascular model for interventional neuroradiology, using either the veins or arteries of the chorionic plate. The HP model has many advantages, including its relatively low cost, minimal infrastructure requirements, and ease of preparation and setup, with fewer ethical concerns compared with animal models. The aim of this translational study was to determine the optimal technique for these distal MTs by assessing first-pass recanalization (FPR), induced arterial collapse, and induced arterial traction, using this HP model.

MATERIALS AND METHODS

Angiogram Procedures, HP Model, and Clots

All procedures were performed with a monoplane angiographic system (Azurion; Philips Healthcare), allowing the acquisition of posterior–anterior 2D projections and 3D rotational angiography after injection of iodinated contrast medium. Iodixanol, 320-mg iodine/mL (Visipaque 320; GE Healthcare), was diluted to 70% with saline and injected manually (8 mL for 2D projections and 20 mL for 3D rotational angiography). All acquired images were converted to internationally compatible DICOM files.

After written consent was obtained from the mothers, 2 placentas were prepared with the methods previously described by our group, using the antiphysiologic direction (ie, using the chorionic plate veins as intracranial arteries). Briefly, the guidewire provided with an 8F introducer sheath was placed in the umbilical vein up to the chorionic plate veins, allowing positioning the introducer sheath with its dilator on this guidewire. The same strategy was used to catheterize each of the umbilical arteries up to the chorionic plate with 5F introducer sheaths. A suture was then placed around each umbilical vessel to avoid fluid reflux along them. A pressure bag was used to deliver a heparinized saline solution via an IV line into the venous introducer, dilating the vessels and removing the intraluminal clots. Another IV line was connected to each arterial introducer, and the other ends were placed in a tray, as the end of the circuit. To avoid any confusion and to allow the use of common terms, we will consider these chorionic plate veins as arteries for the remainder of this article.

Twenty-four clot analogs were generated using the methodology described by Duffy et al to obtain 2 types of clots: red blood cell (RBC)-rich clots, formed after spontaneous coagulation of ovine whole blood, and fibrin-rich clots, formed by mixing citrated plasma with RBCs in a 19:1 ratio (ie, 5% RBCs), which were subsequently coagulated.

MT

According to Saver et al, the intermediate, “medium vessels” can be defined as cerebral arteries with lumen diameters between 0.75 and 2.0 mm. To study the induced arterial collapse and traction on DMVOs produced by the different MT techniques, we therefore performed MTs on vessels of <2.0 mm in diameter. To ensure having vessels with a diameter of <2.0 mm and taking into account the potential random errors induced by the operator and the software, we used only vessels with diameters between 1.5 and 1.7 mm.

Revascularization was conducted by the following: 1) a DA technique with an aspiration catheter (3MAX; Penumbra), and 2) the combined technique with a 3 × 15 mm stent retriever (Catch Mini; Balt Extrusion) and an aspiration catheter (Fargomax; Balt Extrusion). Aspiration was generated by a 60-mL locking syringe (VacLok; Merit Medical). For the DA technique, the aspiration catheter was pushed close to the clot without crossing it with a microwire or microcatheter. We studied 2 positions of the aspiration catheter: in direct contact with the clot and at a distance from it (5–10 mm), simulating cases in which the clot cannot be reached by the aspiration catheter due to the tortuosities of the vessels or angulation. Ten seconds after the start of the manual aspiration, the aspiration catheter was removed. With the distal inner diameter of the 3MAX aspiration catheter being 0.89 mm, the vessel-to-catheter ratio was 1.7 to 1.9. For the combined technique, a microwire (Traxcess 14; MicroVention) and microcatheter (Headway 17; MicroVention) were directed through the clots. The stent was then loaded into the microcatheter and deployed across the clot using the unsheathing technique, with approximately two-thirds of the stent distal to the clot. The aspiration catheter was then guided coaxially along the microcatheter and the stent. In addition, for the combined technique, we studied 2 positions of the aspiration catheter: in direct contact with the clot and at a distance from it (5–10 mm). The stent was allowed to deploy for 5 minutes before removal using the Solumbra technique. An example of MT using the combined technique is shown in Fig 1.

FPR, Arterial Collapse, and Arterial Traction

FPR was defined as achieving a complete recanalization with a single thrombectomy device pass. Failure of FPR was defined by an inability to mobilize the clot or by distal embolization (ie, fragmentation of a primary clot downstream of the primary occlusion).

Possible arterial collapse induced during MT procedures was graded according to the arterial collapse score (ACS) described by Liu et al: ACS 0 when arteries remained unchanged; ACS 1 for indentation (ie, focal inward movement of 1 side of the arterial wall closest to the catheter tip); ACS 2 for flutter (ie, reciprocal cycles of focal collapse and re-expansion of the complete arterial lumen circumference distal to the catheter tip); ACS 3 for focal collapse (ie, sustained collapse of a short segment of the whole arterial lumen into the catheter tip); and ACS 4 for full
collapse (ie, complete collapse of a long segment of the artery extending away from the catheter tip).

Arterial traction was divided into 3 grades: arterial traction score (ATS) 0 for no arterial traction; ATS 1 for local arterial traction (ie, mobilization of the thrombectomized arterial segment only); and ATS 2 for important extended arterial traction with or without avulsion.

**Statistical Analysis**
Categoric variables are presented as count (percentage). Statistical comparisons were performed by the χ² and Fisher exact tests for categoric data. A P value < .05 was considered statistically significant. The data were analyzed using the Statistical Package for the Social Sciences (Version 28.0.1.1; IBM).

**RESULTS**
Two techniques (DA and combined technique), 2 clot types (RBC-rich and fibrin-rich clots), and 2 aspiration catheter positions (direct contact with the clot and at a distance from it [5–10 mm]) were tested with different combinations for a total of 24 procedures. The overall FPR rate was 58.3% (n = 14). Arterial collapse of any type occurred in 87.5% of the cases, with 50.0% ACS 3 (n = 12) and 37.5% ACS 4 (n = 9). We observed no inden- tation (ACS 1) or flutter (ACS 2). Arterial traction of any type also occurred in 87.5%, with 54.2% ATS 1 (n = 13) and 33.3% ATS 2 (n = 8). A detailed table of the results for each procedure is provided in the Online Supplemental Data. Examples of arterial collapse and arterial traction are shown in Fig 2. No contrast media extravasation was observed during the procedures.

**DA versus Combined Technique**
The main results are summarized in the Table. The FPR was less frequent for DA than for the combined technique, without reaching statistical significance (41.7% versus 75.0%, P = .098). ACSs were as follows: 25.0% ACS 0, 75.0% ACS 3, and 0.0% ACS 4 for DA; and 0.0% ACS 0, 25.0% ACS 3, and 75.0% ACS 4 for the combined technique. Full collapse (ACS 4) was significantly less frequent for DA (P = .001).

**Aspiration Catheter Position**
The FPR was more frequent when the aspiration catheter was in direct contact with the clot than when it was at 5–10 mm from the proximal end of the clot, but it did not reach statistical significance (75.0% versus 41.7%, P = .098). ACSs were as follows: 25.0% ACS 0, 33.3% ACS 3, and 41.7% ACS 4 when the aspiration catheter was in direct contact with the clot; and 0.0% ACS 0, 66.7% ACS 3, and 33.3% ACS 4 when it was at 5–10 mm from the proximal end of the clot. Full collapse (ACS 4) was not significantly more frequent for either position of the aspiration catheter. ATSs were as follows: 25.0% ATS 0, 41.7% ATS 1, and 33.3% ATS 2 when the aspiration catheter was in direct contact with the clot; and 0.0% ATS 0, 66.7% ATS 1, and 33.3% ATS 2 when it was at 5–10 mm from the proximal end of the clot. Extended arterial traction (ATS 2) was not significantly more frequent for either position of the aspiration catheter.

For DA, when the aspiration catheter was in direct contact with the clot and the clot completely obstructed the tip of the catheter after the start of the aspiration (n = 3), there was neither collapse nor arterial traction, and in these cases, FPR was always successful (Fig 3). Conversely, when the aspiration catheter was not in direct contact with the proximal aspect of the clot, there was not a single FPR and there was a systematic arterial collapse, resulting in no-flow in the aspiration syringe and a systematic arterial traction. For the combined technique, when the aspiration catheter was at 5–10 mm from the proximal aspect of the clot, FPR occurred in 5 of 6 cases (83.3%), and when the catheter was in direct contact with the clot, FPR occurred in 4 of 6 cases (66.7%).

**Types of Clots**
The FPR was more frequent for fibrin-rich clots than for RBC-rich clots, without reaching statistical significance (75.0% versus 41.7%, P = .098). Of the failed FPRs, fragmentation occurred in 2 cases, with an RBC-rich clot in both cases.
The risk of complications, particularly hemorrhagic ones, is increased for MTs of DMVOs. Arterial collapse and traction induced by thrombectomy devices are phenomena considered potentially responsible for these hemorrhagic complications. However, because DMVOs can be debilitating in some locations, it seems that some distal MTs might be useful for well-selected patients. It is, therefore, necessary to study which techniques are effective and which are the least harmful, especially between DA and the combined technique, which are commonly used for this indication. The HP model is particularly well-suited for these investigations regarding MTs of DMVOs.

The FPR rate was 58.3% in this study, which is consistent with the modified first-pass effect (ie, TICI 2b-3 after a single pass) rates found in the literature (52.4%). In our study, DA was associated with a lower FPR rate than the combined technique, without reaching statistical significance ($P = .098$). This finding is similar to what is found in the literature. Abbasi et al published a meta-analysis regarding PLVOs in 2021, which showed that the modified first-pass effect rates were 48% (1653/3191) for DA and 58% (193/333) for the combined technique. As in our study, these rates were not significantly different ($P = .22$).

In our study dedicated to distal thrombectomies, we observed no indentation (ACS 1) or flutter (ACS 2). Focal or full arterial collapse (ACS 3 or 4) occurred in 87.5% of cases. This result is consistent with the findings of Liu et al, who initially defined 4 stages of arterial collapse for PLVOs but observed ACS 3 or 4 in 98% of cases in the M2 branches. DA was associated with significantly less full arterial collapse ($P < .001$) and extended arterial traction ($P = .001$) than the combined technique. Arterial collapse, especially if full, and arterial traction, especially if extended, are possibly responsible for the high rates of SAH seen during MTs of DMVOs. Thus, because the combined technique appears to be more harmful and even though DA has a probable lower rate of FPR, it seems relevant to try DA as the first-line procedure in thrombectomies of DMVOs.

There was not a single FPR for DA when the aspiration catheter was not in direct contact with the proximal aspect of the clot. The usual way to recognize clot engagement in the aspiration catheter is to activate aspiration and wait until there is no flow in the canister or the aspiration syringe. We have found that arterial collapse also results in a no-flow situation, which can be misinterpreted as clot engagement. Moreover, the aspiration catheter being withdrawn while the arterial wall is being aspirated can cause arterial traction, which can lead to intracranial hemorrhage, without any chance of recanalization. This issue suggests that if the clot cannot be reached with the aspiration catheter, there is little point in trying aspiration alone. For the combined technique, the FPR rates were good regardless of the position of the aspiration catheter (83.3% and 66.7%). Therefore, contrary to DA, it appears relevant to use aspiration in addition to the stent retriever, even if the aspiration catheter cannot reach the clot.

We found that the FPR was more frequent for fibrin-rich clots than for RBC-rich clots, a finding not consistent with findings in the literature. We hypothesized that this finding was due to less interaction between the arterial wall and the clot in this HP model compared with real-world conditions, whereas this interaction in real-world conditions might be more important with fibrin-rich clots compared with RBC-rich clots. This lack of interaction is one of the inherent limitations. In addition, for our experiments, the clots were removed within minutes after placement, whereas in real patients, clot removal is usually performed after several hours. This delay most likely allows greater interaction between the clot and the arterial wall.

While initial stent retrievers had radial diameters of 6 and 4 mm, smaller devices have recently been developed to be more suitable for distal thrombectomies, including 3-mm-diameter devices (eg, the Catch Mini; PrEs et LiTE, phenox; Trevo NXT ProVue, Stryker Neurovascular; and, more recently, Solitaire X, Medtronic) and a 2.5-mm diameter device (eg, the Tigertriever 13; Rapid Medical). For the combined technique in this study,
we used the Catch Mini stent retriever, which has the important advantage of being usable with the 0.017- and 0.013-inch microcatheters.22

One limitation of this study is that the results might have been different with any of the other commercially available stent retrievers. Unfortunately, to the best of our knowledge, there are no studies comparing these devices in terms of safety and effectiveness.

There are a few other limitations we would like to acknowledge. First, in this model, there is no collateral circulation as in the human brain, and extrapolation to human cerebral arteries must be done with caution because arterial collapse might be overestimated. Second, the semitransparent nature of the chorionic plaque is a definite advantage of this model because it allows macroscopic observation of clots and device behavior, but it also allows improved positioning of the aspiration catheter and stent retriever compared with real-world conditions, which may have increased the FPR rate. Third, the ACS (developed by Liu et al17) and ATS scales were developed on the basis of testing in ex vivo models and may not be translatable to patients. Techniques to monitor the mechanical response of arteries in living patients are needed.

### CONCLUSIONS

The combined technique appears to be more harmful, and although DA has a lower rate of FPR, it seems appropriate to try DA as a first-line procedure. However, if the clot cannot be reached by the aspiration catheter, it is not useful and is even risky to try aspiration alone. Conversely, for the combined technique, it seems relevant to use aspiration, even if the aspiration catheter cannot reach the clot. These results need to be confirmed by clinical studies.

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Outcomes with Endovascular Treatment of Patients with M2 Segment MCA Occlusion in the Late Time Window


ABSTRACT

BACKGROUND AND PURPOSE: Randomized trials in the late window have demonstrated the efficacy and safety of endovascular thrombectomy in large-vessel occlusions. Patients with M2-segment MCA occlusions were excluded from these trials. We compared outcomes with endovascular thrombectomy in patients with M2-versus-M1 occlusions presenting 6–24 hours after symptom onset.

MATERIALS AND METHODS: Analyses were on pooled data from studies enrolling patients with stroke treated with endovascular thrombectomy 6–24 hours after symptom onset. We compared 90-day functional independence (mRS ≤ 2), mortality, symptomatic intracranial hemorrhage, and successful reperfusion (expanded TICI = 2b–3) between patients with M2 and M1 occlusions. The benefit of successful reperfusion was then assessed among patients with M2 occlusion.

RESULTS: Of 461 patients, 367 (79.6%) had M1 occlusions and 94 (20.4%) had M2 occlusions. Patients with M2 occlusions were older and had lower median baseline NIHSS scores. Patients with M2 occlusion were more likely to achieve 90-day functional independence than those with M1 occlusion (adjusted OR = 2.13; 95% CI, 1.25–3.65). There were no significant differences in the proportion of successful reperfusion (82.9% versus 81.1%) or mortality (11.2% versus 17.2%). Symptomatic intracranial hemorrhage risk was lower in patients with M2-versus-M1 occlusions (4.3% versus 12.2%, P = .03). Successful reperfusion was independently associated with functional independence among patients with M2 occlusions (adjusted OR = 2.84; 95% CI, 1.11–7.29).

CONCLUSIONS: In the late time window, patients with M2 occlusions treated with endovascular thrombectomy achieved better clinical outcomes, similar reperfusion, and lower symptomatic intracranial hemorrhage rates compared with patients with M1 occlusion. These results support the safety and benefit of endovascular thrombectomy in patients with M2 occlusions in the late window.

ABBREVIATIONS: eTICI = expanded thrombolysis in cerebral infarction; IQR = interquartile range; SICH = symptomatic intracranial hemorrhage

Treatment of medium-vessel occlusion with endovascular thrombectomy is gaining attention among the stroke community. In a recent survey of 366 physicians, 59.2% of participants were willing to treat such patients immediately with endovascular thrombectomy without waiting for the effect of intravenous thrombolysis or the worsening of patient symptoms. These preferences are partly based on evidence from observational studies and meta-analyses suggesting the safety and efficacy of endovascular thrombectomy among patients with medium-vessel occlusion treated within 6 hours from...
symptom onset.2-5 The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration included 130 patients with M2 occlusion and showed the benefit of endovascular thrombectomy compared with medical treatment.2 In addition, multiple prior studies showed similar endovascular thrombectomy benefits among patients with M2 occlusions.3,4

The safety and effectiveness of endovascular thrombectomy in patients with M2 occlusion in the late time window remain unknown. The late-window randomized trials that demonstrated the efficacy and safety of endovascular thrombectomy excluded patients with M2 occlusions. A recent individual patient data meta-analysis of randomized controlled trials of endovascular thrombectomy in the late window included only 15 patients with M2 occlusion of 505 patients.6 Therefore, current guidelines from the American Stroke Association recommend endovascular thrombectomy in the late window in patients with large-vessel occlusions in the M1 segment and the ICA.8,9

Using data from a multicenter international registry, we evaluated the safety and clinical outcomes of endovascular thrombectomy in patients with M2 occlusion presenting between 6 and 24 hours from symptom onset or last known well.

MATERIALS AND METHODS
Data were used from the Selection Of Late-window Stroke for Thrombectomy by Imaging Collateral Extent (SOLSTICE) Consortium, an individual-patient-level analysis of 2 randomized trials and 6 prospective registries from North America, Europe, and South Korea using collateral imaging to select patients eligible for endovascular thrombectomy between 6 and 24 hours after symptom onset or last known well.10 These include the Acute Stroke Registry and Analysis of Lausanne,11 Lausanne, Switzerland; the National Thrombectomy Service Beaumont Hospital Registry,12 Dublin, Ireland; the stroke registry of Turku University Hospital, Turku, Finland; the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial,13 the Safety and Efficacy of Nerinetide in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1) trial,14 the Italian Registry of Endovascular Thrombectomy,15 Italy; the Precise and Rapid Assessment of Collaterals Using Multiphase CTA in the Triage of Patients with Acute Ischemic Stroke for IV or IA Therapy (PRove-IT) study;16 and the Seoul National University Bundang Hospital stroke registry.17 All included studies and registries were approved by local ethics review committees or analyzed only anonymized data as permitted by local legislation. Details regarding the included studies are summarized in the Online Supplemental Data. The pooled analysis of the main study was registered at PROSPERO (No. CRD42020222003).

All patients underwent collateral imaging and were treated with endovascular thrombectomy. Perfusion imaging was performed in a subset of patients according to local institutional protocols. All included studies were approved by the local review board at each participating center.

For this study, we included patients with MCA occlusion and compared patients with M1 occlusions with patients with M2 occlusions. The M2 segment was defined as the segment starting from the first bifurcation of the proximal MCA excluding the anterior temporal branch and ending at the circular sulcus.18

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Online Supplemental Data).

Outcomes
The primary clinical outcome was functional independence defined as mRS ≤ 2 at 90 days. Secondary outcomes were mRS 0–1 at 90 days and safety outcomes, which included mortality within 90 days and the incidence of symptomatic intracranial hemorrhage (SICH) defined according to European-Australian Cooperative Acute Stroke Study 2 (ECASS2) definition.19 Successful reperfusion was defined as expanded TICI (eTICI) ≥2b, corresponding to reperfusion of at least half of the affected arterial territory.

Statistical Analysis
Categoric data were presented as numbers (percentages), and continuous data, as median with interquartile range (IQR). We compared baseline characteristics and outcomes between M1 and M2 occlusion groups using the χ² test for categoric variables and the Mann-Whitney test for continuous variables. Mixed-effects logistic regression was then performed to determine whether M2 occlusion was associated with functional independence after adjusting for age, sex, and time from onset to reperfusion with the data source treated as a random-effects variable. To investigate the differential effect of time from onset to reperfusion on functional independence in patients with M2 versus M1 occlusion, we performed interaction analyses by including the multiplicative interaction term in the regression model.

Furthermore, in patients with M2 occlusions, baseline characteristics were compared between patients who achieved successful reperfusion and those who did not. Because all patients in our data had undergone endovascular thrombectomy, we used successful reperfusion as a proxy for endovascular thrombectomy efficacy, similar to previously published studies.20,21 Mixed-effects logistic regression was attempted to determine the association between successful reperfusion and functional independence at 90 days in the M2 occlusion group after adjusting for age, sex, NIHSS score, and time from onset to reperfusion (“study ID” was included as a random-effects variable). No imputation was performed because missing data were minimal (<5%).

All statistical tests were 2-sided, and P values < .05 were considered significant. Statistical analysis was performed using STATA 17 (StataCorp).

RESULTS
Of 461 patients, 94 (20.4%) had M2 occlusion and 367 (79.6%) had M1 occlusion. The study flow chart is shown in Fig 1.

Baseline demographics, imaging parameters, and outcomes are summarized in Table 1. Compared with patients with M1 occlusion, patients with M2 occlusion were older (75 [median IQR = 63–82] years versus 69 [IQR = 58–78] years, P = .01) and had a lower median NIHSS score (10 versus 16, P < .001) and a higher median ASPECTS (9 versus 8, P < .001). Arterial puncture to reperfusion time was longer in patients with M2 occlusions (median, 45 versus 30 minutes, P = .001). Other workflow times were not significantly different between patients with M2 and M1.
occlusion. Rates of successful reperfusion were similar between the M2 and M1 occlusion groups (82.9% versus 81.1%, \(P = .77\)). The 90-day follow-up was available in 438/461 (95%) patients. The proportion of patients achieving 90-day functional independence (mRS 0–2) was higher in patients with M2 compared with M1 occlusions (59.6% versus 45.0%, \(P = .02\)) (Table 1 and Fig 2). Mortality rates in the patients with M2-versus-M1 occlusion were comparable (11.2% versus 17.2%, \(P = .20\)), while SICH occurred less frequently in the M2 occlusion group (4.3% versus 12.2%, \(P = .03\)) (Table 1). In multivariable analysis adjusting for age, sex, and time from onset to reperfusion, age (adjusted OR = 0.60 per decile increase; 95% CI, 0.51–0.71), time from onset to reperfusion (adjusted OR = 0.94 per 60-minute delay; 95% CI, 0.88–0.99), and M2 occlusion (adjusted OR = 2.13; 95% CI, 1.25–3.65) were independently associated with a higher likelihood of functional independence at 90 days. In the interaction analysis, there was no evidence of the heterogeneity of effect by time from onset to reperfusion when comparing patients with M2-versus-M1 occlusion (\(P_{interaction} = .19\)).

**M2 Subgroup**

Among the 94 patients with M2 occlusion, 89 (95%) had 90-day follow-up data. Functional independence (mRS 0–2) was achieved in 53/89 (59.6%) patients, and successful reperfusion (eTICI \(\geq 2b\)) was seen in 78/94 (83.0%). Patients with successful reperfusion had longer onset-to-reperfusion times (median, 762 [IQR = 586–968] minutes versus 540 [IQR = 511–663] minutes, \(P = .03\)) and higher ASPECTS scores (median 10 [IQR = 8–10] versus median 8.

---

**FIG 1.** Study flow chart for SOLSTICE. The asterisk indicates that 5 patients did not have 90-day follow-up data.

**Table 1: Patient baseline characteristics and outcomes stratified by MCA occlusion location**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M2 Occlusion (n = 94)</th>
<th>M1 Occlusion (n = 367)</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median) (IQR) (yr)(^b)</td>
<td>75 (63–82)</td>
<td>69 (58–78)</td>
<td>0</td>
</tr>
<tr>
<td>Female sex</td>
<td>51 (54.3)</td>
<td>193 (52.6)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake-up stroke</td>
<td>49/93 (52.7)</td>
<td>187/349 (53.6)</td>
<td>19</td>
</tr>
<tr>
<td>Baseline NIHSS (median) (IQR)(^b)</td>
<td>10 (7–15)</td>
<td>16 (11–20)</td>
<td>1</td>
</tr>
<tr>
<td>Tandem cervical occlusion</td>
<td>10 (10.6)</td>
<td>46 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td>IV Alteplase</td>
<td>12 (12.8)</td>
<td>34 (9.3)</td>
<td>0</td>
</tr>
<tr>
<td>Time metrics (median) (IQR) (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from onset to ED door</td>
<td>545 (368–730), [(n = 91)]</td>
<td>538 (405–692), [(n = 342)]</td>
<td>28</td>
</tr>
<tr>
<td>Time from onset to CT scan</td>
<td>579 (416–735), [(n = 91)]</td>
<td>551 (430–710), [(n = 359)]</td>
<td>11</td>
</tr>
<tr>
<td>Time from onset to puncture</td>
<td>744 (485–900), [(n = 87)]</td>
<td>631 (521–815), [(n = 348)]</td>
<td>26</td>
</tr>
<tr>
<td>Time from onset to reperfusion(^b)</td>
<td>762 (530–968), [(n = 85)]</td>
<td>671 (570–848), [(n = 333)]</td>
<td>26</td>
</tr>
<tr>
<td>Time from puncture to reperfusion(^b)</td>
<td>45 (26–64), [(n = 85)]</td>
<td>30 (19–50), [(n = 333)]</td>
<td>25</td>
</tr>
<tr>
<td>Imaging factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPECTSB(^b)</td>
<td>9 (8–10)</td>
<td>8 (7–9)</td>
<td>2</td>
</tr>
<tr>
<td>Use of perfusion imaging</td>
<td>67 (71.3)</td>
<td>223 (60.7)</td>
<td>0</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final TICI 2b–3</td>
<td>78 (82.9)</td>
<td>297 (81.1)</td>
<td>1</td>
</tr>
<tr>
<td>Final TICI 2c–3</td>
<td>29 (30.8)</td>
<td>119 (32.4)</td>
<td>1</td>
</tr>
<tr>
<td>SICH(^b)</td>
<td>4/92 (4.3)</td>
<td>41/337 (12.2)</td>
<td>32</td>
</tr>
<tr>
<td>90-Day mRS (median) (IQR)</td>
<td>2 (1–3), [(n = 89)]</td>
<td>3 (1–5), [(n = 349)]</td>
<td>23</td>
</tr>
<tr>
<td>90-Day mRS = 0–1</td>
<td>36/89 (40.4)</td>
<td>102/349 (29.2)</td>
<td>23</td>
</tr>
<tr>
<td>90-Day mRS = 0–2</td>
<td>53/89 (59.6)</td>
<td>157/349 (45.0)</td>
<td>23</td>
</tr>
<tr>
<td>90-Day mortality</td>
<td>10/89 (11.2)</td>
<td>60/349 (17.2)</td>
<td>23</td>
</tr>
</tbody>
</table>

Note: –ED indicates emergency department.

\(^a\) Values are expressed as median (IQR) or No. (%). Data are for the entire population unless otherwise specified in brackets.

\(^b\) Significant difference between groups.
Effect of Successful Reperfusion in Patients with M2 Occlusion. Patients with successful reperfusion more often achieved 90-day functional independence (48/78, 64.0%) than those with unsuccessful reperfusion (5/16, 35.7%; $P = .07$). Similarly, higher proportions of 90-day mRS 0–1 (44.0% versus 21.4%, $P = .14$) and reduced 90-day mortality (10.7% versus 14.3%, $P = .65$) were seen in successfully reperfused patients. Proportions of SICH were numerically higher but not significantly different in the successful reperfusion group (0% versus 5.3%, $P = .99$) (Table 2).

In multivariable regression analyses adjusting for age, sex, NIHSS score, and time from onset to reperfusion, successful reperfusion was significantly associated with functional independence (adjusted OR = 2.84; 95% CI, 1.11–7.29), 90-day mortality (adjusted OR = 0.13; 95% CI, 0.02–0.67), but not with 90-day mRS 0–1 (adjusted OR = 2.52; 95% CI, 0.82–7.67) (Table 2 and Online Supplemental Data). Regression analysis for SICH was not performed because there was no event in the unsuccessful reperfusion group.

DISCUSSION

In this multicenter international study of patients with stroke presenting in the late window and treated with endovascular

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Table 2: Primary and secondary outcomes in patients with M2 occlusion stratified by successful reperfusion

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Successful Reperfusion (n = 75)</th>
<th>Unsuccessful Reperfusion (n = 14)</th>
<th>$P$ Value</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-Day mRS 0–2</td>
<td>48 (64.0)</td>
<td>5 (35.7)</td>
<td>.07</td>
<td>3.20 (0.97–10.52)</td>
<td>2.84 (1.11–7.29)$^b$</td>
</tr>
<tr>
<td>90-Day mRS 0–1</td>
<td>33 (44.0)</td>
<td>3 (21.4)</td>
<td>.14</td>
<td>2.88 (0.74–11.17)</td>
<td>2.52 (0.82–7.67)</td>
</tr>
<tr>
<td>90-Day mortality</td>
<td>8 (10.7)</td>
<td>2 (14.3)</td>
<td>.65</td>
<td>0.72 (0.13–3.79)</td>
<td>0.13 (0.02–0.67)$^b$</td>
</tr>
<tr>
<td>SICH</td>
<td>4 (5.3)</td>
<td>0 (0.0)</td>
<td>.99</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Note:—En dash indicates that logistic regression was not performed because of the low number of events ($n < 10$).

$^a$ Data on 90-day mRS was missing for 5 patients. Regression analyses were not performed for SICH because the number of events was zero in the unsuccessful reperfusion group. Successful reperfusion was defined as a final eTICI 2b–3. The numbers in parentheses in columns 2 and 3 indicate percentages.

$^b$ Significant results.
thrombectomy, patients with M2 occlusion were more likely to achieve functional independence at 90 days and had a lower risk of SICH compared with patients with M1 occlusion. There were no differences in successful reperfusion rates between the 2 groups. Among patients with M2 occlusion receiving endovascular thrombectomy, successful reperfusion was independently associated with higher rates of functional independence and lower mortality at 90 days. While patients with M2 occlusions are predicted to have less severe initial stroke and therefore better outcomes compared with patients with M1 occlusions regardless of time window, it is relevant that we have empirically shown that there is no evidence of harm in this population of patients in the late window and, indeed, that the direction of effect on clinical outcomes is strongly positive.

There is some evidence supporting the safety and efficacy of endovascular thrombectomy in patients with M2 occlusion in the early window, with a patient-level meta-analysis from the HERMES collaboration showing a beneficial effect of endovascular thrombectomy over best medical care (adjusted OR = 2.39 for mRS 0–2 at 90 days). Evidence regarding the benefit of endovascular thrombectomy in patients with M2 occlusions presenting late is, however, minimal. In this study, we noted higher proportions of successful reperfusion in patients with M2 occlusions than in those reported in the HERMES collaboration (82.9% versus 59.2%) (Fig 2 and Table 3). This difference might be attributed to secular improvement in thrombectomy device technology across the years and the increased experience of neurointerventionalists since 2015, when endovascular thrombectomy became the standard of care.

Rates of functional independence were higher in patients with M2-versus-M1 occlusions in our study. This outcome is both predicted and concordant with a previous meta-analysis of 12 studies in the early time window comparing outcomes in patients with M2-versus-M1 segment occlusions. The rates of functional independence in our study were similar to those reported in patients with M2 occlusion in the HERMES collaboration (59.6% versus 58.2%). Additionally, mortality in patients with M2 occlusions was similar between this study and the HERMES collaboration (11.2% versus 11.9%) (Table 3), suggesting that endovascular thrombectomy of M2 occlusion may be similarly effective and safe in the late window.

The risk of SICH in our patients with M2 occlusion was slightly higher compared with patients with M2 occlusion in the HERMES collaboration (4.3%, 4/92, versus 0.0%; 0/67). However, this risk was significantly lower than that of patients with M1 occlusion in this study. Prior studies in the early time window reported varying results. A meta-analysis of 1080 patients with M2 occlusion found a higher risk of SICH compared with patients with M1 occlusion (15% versus 4.7%). Other studies described a similar or lower risk of SICH in patients with M2-versus-M1 occlusion. The endovascular thrombectomy procedure for M2 occlusions can be technically challenging, given the small size of the vessel, tortuous course, and distal location. This issue was reflected in the longer median procedural times in patients with M2-versus-M1 occlusion in this study (45 versus 30 minutes). However, this difference was not translated into a lower rate of successful reperfusion or 90-day functional independence.

Prior studies identified various predictors of favorable outcomes among patients with M2 occlusion presenting early, with a history of hypertension, baseline NIHSS, prestroke mRS, and time from puncture to reperfusion associated with functional outcome. In this study, age, baseline NIHSS, time from onset to reperfusion, and successful reperfusion were associated with functional outcomes among patients with M2 occlusion. Successful reperfusion was the strongest predictor of functional independence with an adjusted OR of 2.84. A previous multicenter French registry in the early time window showed similar results, with a comparable effect size of successful reperfusion (adjusted OR = 2.79), corroborating our results.

Our study has several limitations. First, we included studies from different centers with varying institutional protocols and inclusion criteria, potentially introducing sampling biases. Second, we did not have a control, non-endovascular thrombectomy arm and, therefore, cannot comment on the outcome of patients with M2 occlusions in the late time window if not treated with endovascular thrombectomy. It is likely that in this retrospective data, only patients with a high likelihood of benefit from endovascular thrombectomy judged by the treating physician were treated. However, our results of patients who were treated in prospective registries were similar to results of the HERMES collaboration, supporting the safety and good outcome among patients with M2 occlusion treated with endovascular thrombectomy in routine practice. Third, procedural techniques or associated complications were not collected in this study. The risk of SICH was, however, low overall. Fourth, information regarding the type of M2 occlusion (proximal-versus-distal, dominant-versus-nondominant) and procedural details such as the number of passes, the use of a stent retriever versus contact aspiration, and general anesthesia versus sedation were not collected in this study, possibly influencing our results. Fifth, the sample size of patients with M2 occlusion was relatively small, precluding subgroup analyses.

**CONCLUSIONS**

In this multicenter international analysis of patients treated with endovascular thrombectomy in the late time window, patients with M2 occlusion achieved better safety and functional outcomes than those with M1 occlusion. The rates of functional independence and mortality are similar to those in prior studies treating M2 occlusions in the earlier time window. These results provide some support for the safety of endovascular thrombectomy in patients with M2 occlusion presenting late after stroke onset or last known well.
REFERENCES

ABSTRACT

BACKGROUND AND PURPOSE: Few studies have reported the utility of high-resolution vessel wall MR imaging in the follow-up of endovascularly treated vertebrobasilar dissecting aneurysms. This study aimed to evaluate the diagnostic performance of high-resolution vessel wall MR imaging combined with TOF-MRA in the follow-up of intracranial vertebrobasilar dissecting aneurysms after reconstructive endovascular treatment.

MATERIALS AND METHODS: Patients with intracranial vertebrobasilar dissecting aneurysms with reconstructive endovascular treatment and followed up with TOF-MRA, high-resolution vessel wall MR imaging, and DSA were included. With DSA as the criterion standard, the diagnostic performance of TOF-MRA, high-resolution vessel wall MR imaging, and high-resolution vessel wall MR imaging combined with TOF-MRA in the evaluation of aneurysm occlusion status and parent artery patency was assessed. Visualization of the stented artery on TOF-MRA and high-resolution vessel wall MR imaging was rated on a 5-point scale.

RESULTS: Twenty-seven patients with 29 aneurysms were included. The sensitivity, specificity, positive predictive value, and negative predictive value of TOF-MRA, high-resolution vessel wall MR imaging, and high-resolution vessel wall MR imaging combined with TOF-MRA for diagnosing aneurysm remnants were 80.0%, 100.0%, 100.0%, and 82.4%; 53.3%, 100.0%, 100.0%, and 66.7%; and 93.3%, 100.0%, 100.0%, and 93.3%, respectively. For the visualization of the stented artery, the mean score of high-resolution vessel wall MR imaging was significantly higher than that of TOF-MRA (4.88 [SD, 0.32] versus 2.53 [SD, 1.25], P < .001). In the evaluation of parent artery patency (normal or pathologic), whereas TOF-MRA had a sensitivity, specificity, positive predictive value, and negative predictive value of 100.0%, 8.0%, 14.8%, and 100.0%, respectively, high-resolution vessel wall MR imaging was completely consistent with the DSA.

CONCLUSIONS: High-resolution vessel wall MR imaging combined with TOF-MRA at 3T showed good diagnostic performance in the follow-up of intracranial vertebrobasilar dissecting aneurysms after reconstructive endovascular treatment.

ABBREVIATIONS: EVT = endovascular treatment; HR-VW-MR imaging = high-resolution vessel wall MR imaging; IMH = intramural hematoma; SPACE = sampling perfection with application-optimized contrasts by using different flip angle evolutions; VBDA = vertebrobasilar dissecting aneurysm; DSA = digital subtraction angiography.
Because of the severe artifacts arising from stents or coils, CTA is seldom used in the follow-up of endovascularly treated intracranial aneurysms. As a noninvasive imaging technique without radiation exposure, TOF-MRA has been widely used in the follow-up of these aneurysms. In VBDAs, compared with sacular aneurysms, the injury of the arterial wall is more complex, and greater attention must be paid to the repair of the injured vessel wall during the follow-up period. Both DSA and MRA depict only geometric shapes of the arterial lumen by blood flow signals but cannot visualize the vessel wall. In contrast, high-resolution vessel wall MR imaging (HR-VW-MR imaging) can reveal the arterial lumen and wall simultaneously by suppressing the flow signals. In our center (First Affiliated Hospital of Nanchang University), HR-VW-MR imaging combined with TOF-MRA has been the most common follow-up imaging technique for intracranial VBDAs. Multiple studies have reported the utility of HR-VW-MR imaging in the diagnosis of intracranial VBDAs. However, few studies have reported the utility of HR-VW-MR imaging in the follow-up of endovascularly treated VBDAs to date. In this study, we aimed to evaluate the diagnostic performance of HR-VW-MR imaging combined with TOF-MRA in the follow-up of intracranial VBDAs treated with reconstructive EVT.

**MATERIALS AND METHODS**

**Ethics Approval**

This study was approved by the ethics committee of First Affiliated Hospital of Nanchang University (Nanchang, China, No. 2020047).

**Patient Cohort**

The local institutional review board (First Affiliated Hospital of Nanchang University) approved this study. Because the study was retrospective, the requirement for written informed consent was waived. Between January 2016 and December 2021, patients with intracranial VBDAs treated with reconstructive EVT and followed up with HR-VW-MR imaging, TOF-MRA, and DSA in our center were included. If the interval between HR-VW-MR imaging and the DSA examination was >2 weeks, the patient was excluded. Patients’ baseline and treatment information was acquired from the medical record system.

**Image Acquisition**

The MR imaging examination was performed on a 3T system (Magnetom Skyra; Siemens) with a 20-channel head and neck united coil. A TOF-MRA was performed first. HR-VW-MR imaging included pre- and postcontrast 3D T1-weighted sampling perfection with application-optimized contrasts by using different flip angle evolutions (SPACE) sequences. Postcontrast images were obtained 5 minutes after venous injection of single-dose (0.1 mmol/kg) gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals) with the same parameters as for the precontrast T1-weighted images. The scanning range included the whole brain. The scan parameters are listed in Table 1.

With transfemoral catheterization, EVT and follow-up DSA were performed with the following angiographic systems: UNIQ FD20/15 (Philips Healthcare) or Axiom Artis dFA (Siemens).

**Image Analysis**

All images were reviewed blindly in random order by 2 interventional neuroradiologists with >10 years’ experience. Only the locations of the treated aneurysms were provided to the reviewers. TOF-MRA and HR-VW-MR imaging were reviewed separately with an interval of 1 month. For TOF-MRA, both MIP images and source images were reviewed. For 3D T1 SPACE, MRPs were performed in the axial and oblique sagittal directions to visualize VBDAs from different planes. The image quality of the stented artery on TOF-MRA and HR-VW-MR imaging was rated on the following 5-point scale: 1) not visible (the arterial structure was invisible, and strong artifacts were present); 2) poor (structures were slightly visible, and substantial artifacts or blurring was present); 3) acceptable (the diagnostic quality was acceptable, and moderate artifacts or blurring was present); 4) good (the images were of good quality, and minimal artifacts or blurring was present); and 5) excellent (the depiction was nearly equal to that of DSA). In cases of disagreement, the scores of the 2 reviewers were averaged. The patency of the parent artery was divided into 3 grades (normal, stenosis, or occlusion) or 2 grades on a simplified scale (normal or pathologic [stenosis or occlusion]). The aneurysm occlusion status was classified as complete or incomplete occlusion. Complete occlusion was defined by an absence of contrast agent in the aneurysmal sac observed on DSA, no flow signal in the aneurysmal sac on TOF-MRA, or no flow void in the aneurysmal sac on HR-VW-MR imaging. Otherwise, the aneurysm was considered incomplete occlusion. In cases of discrepancy, a consensus was reached between the reviewers by discussion.

After another month, the TOF-MRA and HR-VW-MR imaging findings were again reviewed together. After the diagnostic information from TOF-MRA and HR-VW-MR imaging was combined, the aneurysm occlusion status and parent artery patency were assessed. In cases of discrepancy, a consensus was reached by discussion.

DSA images were reviewed 1 month later by the same reviewers without knowledge of the MR imaging results. The evaluation included the aneurysm occlusion status and parent artery patency with the same classification standard used for the MR imaging examinations.

To investigate the vessel wall features of VBDAs after procedures, the presence of an intimal flap, double lumen sign, or intramural hematoma was reviewed on HR-VW-MR imaging. An intimal flap was defined as a linear layer crossing the arterial lumen that extended to the sidewall. The double lumen sign was

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**Table 1: Imaging parameters of MR imaging sequences**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>TOF-MRA</th>
<th>3D T1-Weighted SPACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR (ms)</td>
<td>21</td>
<td>900</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>3.43</td>
<td>16</td>
</tr>
<tr>
<td>Flip angle</td>
<td>18°</td>
<td>–</td>
</tr>
<tr>
<td>FOV (mm)</td>
<td>180 × 180</td>
<td>200 × 200</td>
</tr>
<tr>
<td>Matrix</td>
<td>320 × 320</td>
<td>384 × 384</td>
</tr>
<tr>
<td>No. of excitations</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Section thickness (mm)</td>
<td>0.55</td>
<td>0.53</td>
</tr>
<tr>
<td>No. of slices</td>
<td>162</td>
<td>256</td>
</tr>
<tr>
<td>Echo-train length</td>
<td>–</td>
<td>293</td>
</tr>
<tr>
<td>Scanning time (min)</td>
<td>4:05</td>
<td>9:18</td>
</tr>
</tbody>
</table>

**Note:** The en dash indicates not applicable.
Table 2: Evaluation of aneurysm occlusion status with different imaging modalities

<table>
<thead>
<tr>
<th></th>
<th>DSA</th>
<th>TOF-MRA combined with HR-VW-MR imaging</th>
<th>HR-VW-MR imaging</th>
<th>InCO</th>
<th>CO</th>
<th>Total</th>
<th>( \kappa ) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOF-MRA</td>
<td></td>
<td></td>
<td></td>
<td>0.794 (0.579–1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>InCO</td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>3</td>
<td>14</td>
<td></td>
<td>0.525 (0.255–0.794)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>14</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td>0.931 (0.799–1.0)</td>
</tr>
</tbody>
</table>

Note: InCO indicates complete occlusion; InCO, incomplete occlusion.

defined as 2 lumens represented as 2 jets of flow void within 1 vessel. An intramural hematoma was identified as a false lumen filled with hematoma.

Statistical Analysis

All statistical analyses were performed in SPSS 26.0 (IBM) and SAS 9.4 (SAS Institute). Quantitative variables are expressed as mean (SD) or median (interquartile range), and qualitative variables are presented as counts (percentages). The aneurysm size is expressed as (the Maximum Diameter Perpendicular to the Parent Artery) \( \times \) (the Length of Lesion along the Parent Artery) on preoperative DSA. Interobserver and intermodality consistency, specificity, positive predictive value, and negative predictive value of TOF-MRA, HR-VW-MR imaging, and HR-VW-MR imaging combined with TOF-MRA were calculated. \( P < .05 \) was considered significant.

RESULTS

Patient and Aneurysm Characteristics

Twenty-seven patients (5 women, 22 men; mean age, 48.7 [SD, 10.3] years; range, 25–66 years) with 29 intracranial VBDAs were included in this study. Among those patients, 25 patients had 1 aneurysm, and 2 patients had 2 aneurysms. Twelve (41.4%) aneurysms ruptured before the procedures. The distribution of these aneurysms was as follows: basilar artery, 3 (10.3%); left vertebral artery, 12 (41.4%); right vertebral artery, 13 (44.8%); and vertebrobasilar junction, 1 (3.4%). The average size of these aneurysms was 7.7 (SD, 2.2) \( \times \) 13.7 (SD, 5.3) mm. The 29 aneurysms were treated as follows: 24 with stent-assisted coiling (single LVIS, MicroVention, 17; single Enterprise, Codman & Shurtleff, 2; double LVIS, 1; double Enterprise, 2; LVIS + Enterprise, 2), 1 with double LVIS without coils, 1 with single Tubridge (MicroPort Medical Company) with coiling, 2 with a single Pipeline (Medtronic) alone, and 1 with a double Pipeline without coils. All coils used in this study were bare platinum coils. Seven (24.1%) aneurysms were completely occluded, and 22 (75.9%) aneurysms were incompletely occluded immediately after treatment. The median interval between the procedures and MR imaging examinations was 191 days (range, 49–1128 days; interquartile range, 129–273 days).

Aneurysm Occlusion Status

The assessment of aneurysm occlusion status with different imaging modalities is summarized in Table 2. DSA showed 14 (48.3%) aneurysms with total occlusion and 15 (51.7%) with incomplete occlusion. TOF-MRA and DSA were discordant for 3 (10.3%) aneurysms that showed incomplete occlusion on DSA but were classified as complete occlusion with TOF-MRA (\( \kappa = 0.794 \)). HR-VW-MR imaging and DSA were discordant for 7 (24.1%) aneurysms that showed incomplete occlusion on DSA but were classified as complete occlusion with HR-VW-MR imaging (\( \kappa = 0.525 \)). However, only 1 (3.4%) aneurysm was discordant between HR-VW-MR imaging combined with TOF-MRA and DSA (\( \kappa = 0.931 \)). One aneurysm treated with 2 Pipeline implantations, with small remnants visible on DSA, was classified as complete occlusion on HR-VW-MR imaging combined with TOF-MRA. Figures 1–3 show representative images.

The comparative diagnostic performance of different imaging modalities is shown in Table 3. Whereas TOF-MRA and HR-VW-MR imaging showed a sensitivity and specificity of 80.0% and 100.0% and 53.3% and 100.0%, respectively, HR-VW-MR imaging combined with TOF-MRA showed a sensitivity and specificity of 93.3% and 100.0%, respectively.

Patency of the Parent Artery

The mean image quality score of HR-VW-MR imaging was significantly higher than that of TOF-MRA (4.88 [SD, 0.32] versus 2.53 [SD, 1.25], \( P < .001 \)). Although all HR-VW-MR images had good or excellent image quality (score, ≥4), only 31.0% (9/29) of the TOF-MRA images had good or excellent image quality. When the TOF-MRA and HR-VW-MR images were reviewed together, all assessments of the patency of the parent artery were made on the basis of the HR-VW-MR images in this study because the HR-VW-MR imaging provided a better view of the arterial lumen than TOF-MRA in all cases. Four (14.8%) patients showed mild motion artifacts on HR-VW-MR imaging, whereas no motion artifacts were found in TOF-MRA. The motion artifacts were presumed to have been caused by oral motion and had little influence on image quality.

DSA indicated that 25 (86.2%) patients had a normal parent artery, and 4 (13.8%) patients had mild parent artery stenosis (<50%). TOF-MRA indicated that 2 (6.9%) patients had a normal parent artery, 18 (62.1%) patients had parent artery stenosis, and 9 (31.0%) patients had parent artery occlusion. TOF-MRA and DSA were discordant for 23 (79.3%) patients (\( \kappa = 0.088 \)). Nineteen normal parent arteries on DSA were classified as stenosis with TOF-MRA, and 4 other normal parent arteries on DSA were classified as occlusion with TOF-MRA. With the simplified 2-grade scale, the intermodality agreement between DSA and TOF-MRA was 0.023.
The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of TOF-MRA were 100.0%, 8.0%, 14.8%, 100.0%, and 20.7%, respectively. However, regardless of whether the simplified 2-grade scale or the 3-grade scale was used, the assessment results based on HR-VW-MR imaging were completely consistent with those based on DSA. Therefore, the intermodality agreement was 1.00.

**Evaluation of the Vessel Wall**

The presence of an intimal flap, double lumen sign, and intramural hematoma (IMH) was observed in 2 (6.9%), 3 (10.3%), and 17 (58.6%) patients, respectively. All intimal flaps and double lumen signs were observed in incompletely occluded aneurysms. Intramural hematomas were observed in 42.9% (6/14) of completely occluded aneurysms and 73.3% (11/15) of incompletely occluded aneurysms, respectively ($P = .139$). Contrast enhancement of the affected vessel wall and intimal flaps was observed in all the cases.

**Interobserver Agreement**

In the evaluation of the aneurysm occlusion status, the $\kappa$ value of interobserver agreement for TOF-MRA, HR-VW-MR imaging, HR-VW-MR imaging combined with TOF-MRA, and DSA was 0.86, 0.83, 1.00, and 0.93, respectively.

In the assessment of the patency of the parent artery with the 3-grade scale, the $\kappa$ value for TOF-MRA, HR-VW-MR imaging, HR-VW-MR imaging combined with TOF-MRA, and DSA was 0.88, 0.84, 0.84, and 0.84, respectively. With the simplified 2-grade scale, the $\kappa$ value for TOF-MRA, HR-VW-MR imaging, HR-VW-MR imaging combined with TOF-MRA, and DSA was 0.65, 0.84, 0.84, and 0.84, respectively.

**DISCUSSION**

This study demonstrated that HR-VW-MR imaging combined with TOF-MRA at 3T had high concordance with DSA in the
evaluation of aneurysm occlusion status and the patency of the parent artery in the follow-up of intracranial VBDAs after reconstructive EVT. For visualization of the stented artery, HR-VW-MR imaging provided obviously better image quality than TOF-MRA. The interobserver agreement in the image analysis for different imaging modalities ranged from substantial to almost perfect.

**Aneurysm Occlusion Status**

The aneurysm occlusion status and patency of the parent artery were the 2 major concerns in the follow-up of VBDAs. Because TOF-MRA used bright-blood technology to depict the blood flow, the blood flow in the parent artery and residual aneurysm showed high signals, which were distinguishable from those of the surrounding tissues. In contrast, to depict the vessel wall and lumen directly, black-blood technology was used in HR-VW-MR imaging. Because the blood flow signals were suppressed in HR-VW-MR imaging, the residual aneurysm was sometimes difficult to distinguish from surrounding tissues (Fig 1). In general, TOF-MRA was superior to HR-VW-MR imaging in the evaluation of aneurysm occlusion status in our study. However, HR-VW-MR imaging was less sensitive to the susceptibility artifacts caused by stents and coils than TOF-MRA, and the vessel wall features on HR-VW-MR imaging might be helpful in assessing aneurysm occlusion status. Figure 3 shows the follow-up images of a vertebral artery dissecting aneurysm treated with Enterprise stent-assisted coiling. Whereas the residual aneurysm and most of the stented artery were invisible on TOF-MRA because of artifacts, the HR-VW-MR imaging showed a fusiform dilation of the parent artery, similar to the DSA findings. The aneurysm was classified as having incomplete occlusion on 3D TI-weighted SPACE. The postcontrast image shows mild enhancement of the stented artery. The image quality score for TOF-MRA and 3D TI-weighted SPACE is 1/1 and 5/5, respectively.

**Table 3: Diagnostic performance of TOF-MRA, HR-VW-MR imaging, and HR-VW-MR imaging combined with TOF-MRA in the assessment of aneurysm occlusion status**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOF-MRA</td>
<td>80.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>82.4%</td>
<td>89.7%</td>
</tr>
<tr>
<td>HR-VW-MR imaging</td>
<td>53.30%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>66.7%</td>
<td>75.9%</td>
</tr>
<tr>
<td>HR-VW-MR imaging combined with TOF-MRA</td>
<td>93.3%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>93.3%</td>
<td>96.6%</td>
</tr>
</tbody>
</table>

**FIG 3.** Follow-up images of a left vertebral artery dissecting aneurysm treated with Enterprise stent-assisted coiling at the sixth month postoperatively. A, DSA shows fusiform dilation (white arrows) of the left vertebral artery. The aneurysm is diagnosed as having incomplete occlusion. Arrowheads indicate the stent edges. B, The MIP image of TOF-MRA shows strong signal loss at the stented artery. The aneurysm remnant is not depicted. C and D, Pre- and postcontrast 3D TI-weighted SPACE shows a fusiform dilation of the parent artery, similar to the DSA findings. The aneurysm is classified as having incomplete occlusion on 3D TI-weighted SPACE. The postcontrast image shows mild enhancement of the stented artery. The image quality score for TOF-MRA and 3D TI-weighted SPACE is 1/1 and 5/5, respectively.
VBDAs may pose greater risk than saccular aneurysms in embolization with coils. The relatively looser coil packing resulted in fewer susceptibility artifacts caused by coils.

**Patency of the Parent Artery**
The image quality of the stented artery on TOF-MRA was disappointing because TOF-MRA was sensitive to the susceptibility artifacts and radiofrequency shielding artifacts of implanted stents or flow diverters. Consequently, TOF-MRA often showed false stenosis or occlusion of the stented artery (Figs 1 and 3).\(^{11,12}\) In contrast, HR-VW-MR imaging showed significantly better image quality than TOF-MRA, with no or few artifacts. This result was consistent with findings from a previous study demonstrating that 3D T1-weighted SPACE was more accurate than TOF-MRA in the assessment of patency of the stented artery in 53 intracranial aneurysms treated with the Pipeline.\(^{13}\) In this study, regardless of whether the simplified 2-grade or 3-grade scale was used, the HR-VW-MR imaging had a 100% coincidence rate with DSA in the evaluation of the patency of the parent artery. Therefore, HR-VW-MR imaging is a good technique for assessing the patency of the parent artery in intracranial VBDAs treated with reconstructive EVT.

**Evaluation of Vessel Walls**
Beyond the aneurysm occlusion status and the patency of the parent artery, attention should also be paid to arterial wall evolution during the follow-up period. In this study, whereas an intimal flap and double lumen sign were observed only in incompletely occluded aneurysms, IMH was observed in both completely occluded and incompletely occluded aneurysms. Complete occlusion of the aneurysms indicated an absence of blood flow into the vessel wall through the ruptured internal elastic lamina but did not indicate that the affected vessel wall was healing well. Tian et al\(^{14}\) reported that persistent high signal intensity of IMHs may be associated with the progression of intracranial VBDAs after reconstructive EVT. Zhang et al\(^{15}\) reported 3 VBDAs that were confirmed to have total occlusion on DSA and showed IMH enlargement on MR imaging. Even if the parent arteries are sacrificed, the IMH might continue to enlarge; however, the mechanism is unclear in this circumstance.\(^{15}\) Some authors have speculated that the rupture of the vasa vasorum in the arterial wall results in IMH recurrence.\(^{16,17}\) Therefore, for patients with treated VBDAs whose symptoms persist or worsen, an HR-VW-MR imaging examination is recommended even if the DSA shows that the aneurysms involve total occlusion.

Zhang et al\(^{18}\) have reported that aneurysm wall enhancement of unruptured VBDAs on HR-VW-MR imaging before procedures might predict an unstable state and can be used to predict aneurysm progression after reconstructive EVT. A study including 53 intracranial saccular aneurysms has reported that aneurysm wall enhancement is commonly observed after embolization and decreases with time.\(^{19}\) However, no study on affected vessel wall enhancement in VBDAs after reconstructive EVT has been reported. In our study, the affected vessel wall enhancement was observed in all cases. The association between the degree of affected vessel wall enhancement and the stability of VBDAs after reconstructive EVT and the change in vessel wall enhancement with time will be explored in our future studies.

**Imaging Protocol**
Although HR-VW-MR imaging can be acquired with both 2D and 3D sequences, only the 3D T1-weighted SPACE sequence was performed in this study. The 2D sequences can provide high spatial resolution and a good SNR but require longer acquisition times than 3D sequences when the VBDAs are large.\(^{1}\) In contrast, 3D T1-weighted SPACE using isotropic volume scanning can cover a large scope in a relatively short scanning time. In addition, the vessel wall and lumen can be observed from different projections through MPR of 3D SPACE. The major limitation of HR-VW-MR imaging is its relatively long scanning time. The total examination time in our study was nearly 20 minutes. Therefore, the HR-VW-MR imaging examination is not suitable for patients with claustrophobia or postoperative restlessness. To decrease the examination time, we changed the imaging protocol of HR-VW-MR imaging from 2022: First, TOF-MRA was performed to define the location of the vertebrobasilar artery; then, the scanning scope of 3D T1-weighted SPACE was limited to the location of the vertebrobasilar artery. This imaging protocol decreased the examination time by nearly half.

Owing to the high signal intensity of the contrast agent, contrast-enhanced MRA has been reported to be superior to TOF-MRA in the assessment of aneurysmal occlusion status for endovascularly treated intracranial aneurysms.\(^{11,20}\) In recent years, Silent MRA (GE Healthcare) and pointwise encoding time reduction with radial acquisition subtraction-based MRA (PETRA; Siemens), both using an arterial spin-labeling combined with an ultrashort TE technique, have been demonstrated to be superior to TOF-MRA in the evaluation of aneurysm occlusion status for endovascularly treated aneurysms.\(^{10,20,22}\) Given that most treated intracranial aneurysms in these previous studies were saccular aneurysms, the diagnostic performance of these MRA techniques should be compared in intracranial VBDAs treated with reconstructive EVT in future studies. Because all MRA techniques are unable to provide a precise assessment of the affected arterial wall, HR-VW-MR imaging is always recommended in the follow-up of treated VBDAs.

**Limitations**
This article had several limitations: First, it was a retrospective study with a small sample size. Second, the exact sizes of dissecting aneurysms should be measured on the 3D SPACE images. Because some patients did not undergo HR-VW-MR imaging before their procedures, the aneurysmal size was measured on the DSA images during their procedures. The exact size of the VBDAs might have been larger because the IMHs could not be visualized on DSA images. Finally, the interval between the procedures and MR examinations varied widely among patients.

**CONCLUSIONS**
In the follow-up of intracranial VBDAs after reconstructive EVT, HR-VW-MR imaging combined with TOF-MRA at 3T showed good diagnostic performance in the evaluation of aneurysm occlusion status and patency of the parent artery. As a noninvasive imaging technique, the combination of HR-VW-MR imaging and TOF-MRA may be an ideal option for repeat
examinations in patients with intracranial VBDAs after reconstructive EVT.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES

The natural history of intracranial aneurysms (IAs) is poorly understood, and there is significant variability in their management.1-3 Increasing use of noninvasive, cross-sectional imaging leads to frequent diagnosis of incidental, small unruptured aneurysms. Unfortunately, their rupture risk is not well-known, and there are no clear guidelines regarding which aneurysms should be treated or the optimal frequency and duration of subsequent surveillance studies.4,5 In addition, recommendations for screening high-risk populations for IAs should take into consideration the higher baseline prevalence suggested in more recent studies compared with historical publications.6,7 Ruptured aneurysms, however, are associated with very high morbidity and mortality.8 Lack of timely diagnosis and treatment can be a source of poor outcome and, potentially, malpractice claims.9

Fear of litigation and rising malpractice premiums may encourage defensive medicine practices, including administration of superfluous tests or aggressive use of preventive treatments.10 In a 2012 survey of >1000 practicing neurosurgeons in the United States, 72% reported ordering additional imaging studies in an effort to reduce the perceived risk of medical malpractice claims.11 This approach has huge health and economic implications and may lead to increased physician frustration and burnout.12 An estimated $60 billion of the nearly $3 trillion annual health care expenditure in the United States is attributed to defensive medicine practices.9

The high financial and emotional costs of lawsuits create a need to understand the medicolegal risks associated with IAs. This requires an awareness of previous lawsuits associated with
the diagnosis and management of IAs and the clinical settings in which they are most likely to arise. This study aimed to characterize the causes, distribution, and nature of malpractice litigation related to the diagnosis and treatment of IAs in the United States.

MATERIALS AND METHODS

No ethics approval was required for this study because no sensitive data were used and all materials were collected from open, published sources. Two online legal data repositories, VerdictSearch (American Lawyer media; https://www.linkedin.com/company/the-american-lawyer) and LexisNexis (RELX; https://www.relx.com/our-business/market-segments/legal) were screened to identify jury awards and settlements related to medical malpractice involving patients with IAs. Information was collected from all jurisdictions, ie, all 50 states and Washington, DC, from January 1, 2000, to December 31, 2020, and the most recently available published court determinations were included. These 2 legal research platforms collectively contain >1.1 million published summaries of jury awards and settlements. Furthermore, they both provide detailed information regarding plaintiff and defendant characteristics, causes of action, list of plaintiff and defendant experts, injury reports, award breakdowns, and other facts of the case. Claims that were dismissed before proceeding to trial or settled out of court, however, are not available in these databases. Both databases were queried using the terms “cerebral” and “aneurysm,” and only those cases categorized as “medical malpractice” or “wrongful death” were included. Only those cases in which claims of negligence were made against a doctor and/or a health care institution (including clinics, privately owned hospitals, private radiology firms, and university hospitals) were included. Claims were further categorized as failure to diagnose despite reasonable suspicion, failure to treat, failure to transfer, complications during the treatment of aneurysms, and failure in acquiring proper informed consent. Cases against corporations or doctors prescribing over-the-counter medications that may have indirectly led to aneurysmal rupture were not included (eg, prescription of antihistamines with phenylpropanolamine leading to hypertension and eventual aneurysmal rupture). Cases in which there was a claim made against paramedics or firemen for inappropriate diagnoses or treatments were not included. Finally, claims of negligence and indirect causes of aneurysmal rupture by health care professionals were not included (ie, a nurse practitioner assaulted a patient in the head leading to aneurysmal rupture).

Relevant factors were identified and collected after analysis of each case summary. Such factors included the year of publication of the trial, location of the trial, defendant and plaintiff characteristics, health care setting, case outcomes, award amounts, reasons for the lawsuit/claim, and category of negligence or medical malpractice, eg, failure to diagnose. There were a few cases in which the method of resolution was mixed when multiple parties were involved, ie, 1 plaintiff victory and 1 case dismissal; in such cases, it was counted as 1 plaintiff victory. Descriptive statistics were used for data analysis when appropriate.

RESULTS

Case Details

Case Characteristics. LexisNexis and VerdictSearch returned 287 published case summaries. After screening for inclusion and exclusion criteria and removal of duplicate studies, 133 unique case summaries were identified and included in the analysis (Fig 1). Twenty-seven states were represented, with most of the cases coming from New York (31, 23%), California (15, 11%), and Pennsylvania (11, 8%). Jurisdictions at the federal and state level were included (Online Supplemental Data).

Plaintiff Characteristics. The average age of the plaintiff at the time of the judgment was 47 years (range, 2 weeks to 76 years of age). Only 2 pediatric cases were noted.

Defendant Characteristics. Of 133 case summaries, 159 physicians were sued for medical malpractice, of which 125 (79%) were men, 12 (7%) were women, and 22 (14%) were unidentified. In 60/133 (45%) cases, claims were made against at least 1 doctor.
and no health care facility. In another 60/133 (45%) cases, claims were made against both a physician and a health care facility. In 13/133 (10%) cases, claims were made against a health care facility only.

**Defendant Specialties.** After analysis of the case summaries, physicians from several specialties were found to be involved in litigation. Claims of malpractice were made against neurosurgeons (29/159, 18%), emergency medicine physicians (27/159, 17%), primary care providers (26/159, 16%), diagnostic/nonspecified radiologists (18/159, 11%), interventional neuroradiologists (7/159, 4%), a diagnostic neuroradiologist (1/159, 0.6%), neurologists (18/159, 11%), and anesthesiologists (5/159, 3%). Less frequently named specialists included ophthalmologists, otolaryngologists, and vascular surgeons. The defendant specialties are presented in Fig 2, and a summary of the malpractice allegations against the 5 most common specialties is presented in Table 1.

**Health Care Facility Involvement.** There were 75 unique health care facilities involved in 73 cases. Forty-five of 75 (60.0%) health care facilities were identified as private hospitals/clinics, 22/75 (30%) were identified as university-affiliated or university hospitals, 7/75 (9%) were identified as private radiology clinics, and there was 1 claim made against the Office of Veteran Affairs.

**Radiology-Specific Analysis.** Twenty-six radiologists were involved in a malpractice suit. Eighteen of 26 (69%) were diagnostic/nonspecified radiologists, 7/26 (27%) were neurointerventional radiologists, and there was 1 (4%) neuroradiologist. Sixteen of 18 (89%) diagnostic radiologists and 1 neuroradiologist
allegedly “failed to correctly interpret aneurysm evidence on CT or MR imaging.” Two of 18 (11%) diagnostic radiologists allegedly “failed to timely schedule a patient for imaging.” Six of 7 (86%) neurointerventional radiologists allegedly “failed to adequately treat due to procedural error during a diagnostic or treatment intervention.” Procedural errors included 5/6 (83%) cases of an attempted coiling with resultant perforation and rupture of an unruptured aneurysm, and 1 (17%) case of “misdiagnosis of an aneurysm as a junctional dilation on cerebral arteriography and failure to treat that aneurysm.” Last, 1/7 neurointerventional radiologists allegedly “failed to timely treat and unnecessarily delay a neuro-interventional procedure.” 

A summary of the malpractice allegations against the 5 most common specialties and a summary of the settlement and trial outcomes for radiologists is presented in Tables 1 and 2, respectively.

<table>
<thead>
<tr>
<th>Causes of Action</th>
<th>Failure to Diagnose</th>
<th>Failure to Timely Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to diagnose</td>
<td>Failure to work-up category went to trial, with 12/20 (60%) judgments for the defense and 8/20 (40%) for the plaintiff. Eight of 30 (27%) cases settled, of which 5/8 (63%) cases settled for a specific dollar amount and 3/8 (37%) settled for a confidential/undisclosed amount.</td>
<td>In the failure to correctly interpret a CT or MR imaging category, 16/17 (94%) cases involved diagnostic/nonspecified radiologists and 1/17 (6%) physicians was specified as a neuroradiologist. Fifteen of 17 (88%) incorrect interpretation cases were on CT, and 2/17 (12%) were on MR imaging. Five of 17 (29%) cases occurred in the outpatient setting, and 2/17 (12%), in the emergency setting; the rest of the cases (10/17, 59%) did not specify the radiology setting. Nine of 17 cases (53%) were resolved by settlements, and 5/9 (55%) settlements specified the amount awarded to the plaintiff, while 4/9 (45%) settlements were confidential/undisclosed. Six of 17 (35%) cases went to trial, with 4/6 (67%) trials resulting in judgments for the defense and 2/6 (33%) trials resulting in judgments for the plaintiff. The plaintiffs were awarded $4,000,000 and $43,000,000, respectively. Last, 2/17 (12%) cases were dismissed.</td>
</tr>
</tbody>
</table>
| Failure to treat | There were 4 medical malpractice claims relating to the inability or failure to timely transfer a patient for a procedure or imaging that was necessary for diagnosis/work-up of an IA. In most of these cases, there was a high suspicion of IA rupture. In 1/4 (25%) cases, there was a failure to schedule imaging due to a delay in finding an oversized MR imaging machine for a morbidly obese patient. In another case, the plaintiffs claimed that there was a failure to properly triage, and an inappropriate delay in imaging. In 2/4 (50%) cases, there was an inability to transfer a

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**Table 2: Settlement and trial outcomes for radiologists**

<table>
<thead>
<tr>
<th></th>
<th>Settlements</th>
<th>Trials Won</th>
<th>Trials Lost</th>
<th>Dismissals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic radiologists</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Neurointerventional radiologists</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuroradiologist</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**FIG 3.** A, Award amounts in failure-to-treat cases resolved by trial. B, Award amounts in failure-to-treat cases resolved by settlement.
patient due to unavailable beds caused by patient overflow. Three of 4 (75%) cases went to trial, resulting in awards for the plaintiff of $9,000,000, $8,000,000, and $112,000,000, respectively. There was 1 case that was settled for $450,000.

Failure to Refer. Last, there were 4 medical malpractice claims made against primary care providers and their inability to timely refer the patient to a neurology specialist. Primary care providers included internal medicine physicians and family medicine practitioners. Two of 4 (50%) were resolved at trial with 1 judgment for the defense and 1 for the plaintiff, with an award of $1,500,000. Two of 4 (50%) cases were resolved by settlement, in the amounts of $3,600,000 and $450,000, respectively.

The causes of action related to treatment of aneurysms are detailed in the Online Supplemental Data.

There were 37 cases related to failure to treat an IA and 24 that were related to surgical procedures or postoperative complications (4 of these were for ruptured IAs and 9 for unruptured IAs, and 11 were non-specific). There were 3 cases in which the defendant physicians diagnosed an unruptured cerebral aneurysm and scheduled follow-up for a procedure or further imaging at a later date. However, in all 3 cases, the diagnosed aneurysm ruptured before the scheduled follow-up. Two of these cases were settled when plaintiffs were awarded $150,000 and $3,600,000, respectively.

Judgment Awards and Settlements
One hundred thirty-three cases were identified from 2000 to 2020. Fifty-two of 133 (39%) of these cases resulted in settlement, and 70/133 (53%) cases went to trial. Nine of 133 (7%) cases were dismissed without a trial, and there were 2/133 (1.5%) cases in which the method of resolution was mediation. There was only 1 case in which the awarded amount had to be reduced to the statutory cap ($7,000,780 reduced to $2,050,000).

Of the cases that went to trial (Fig 4A), 44/70 (63%) cases resulted in a judgment for the defendant and 26/70 (37%) cases resulted in a judgment for the plaintiff, with an average award of $12,620,953 (range, $0–$112,000,000). Of the 52 cases that were settled (Fig 4B), 35/52 (67%) cases were settled for an undisclosed or confidential dollar amount. Seventeen of 52 (33%) cases provided specific information regarding settlement amounts. The average settlement amount was $1,491,928 (range, $25,000–$4,350,000).

Incidence of Lawsuits Relative to the Stage of Care Delivery
The highest incidence of lawsuits occurred in the primary and emergency care settings (Fig 5). We identified 31/133 (23%) claims of medical malpractice occurring in the primary care
setting; the most common cause of action consisted of a nonspecific failure to diagnose (14/31, 45%) or a failure on the part of a primary care provider to include unruptured or ruptured IA as one of the differential diagnoses for vague presentations, thus a failure to perform further work-up (12/31, 39%). We also found 5/31 (16%) cases of failure to correctly identify an unruptured intracranial aneurysm in an outpatient setting by a radiologist, with subsequent rupture of the aneurysm. Thirty of 133 (22%) claims of medical malpractice were in the emergency care setting; almost all the claims were against emergency medicine physicians (26/30, 87%). Only 2/28 (7%) cases in the emergency setting were due to failure on the part of the radiologist to identify a ruptured IA in an emergency setting.

**DISCUSSION**

Our review of 2 large legal databases resulted in 133 unique malpractice claims between 2000 and 2020 filed in 27 states in the United States relating to patients with IAs. One hundred fifty-nine physicians were sued in 120/133 cases, most frequently involving United States relating to patients with IAs. One hundred fifty-nine practice claims between 2000 and 2020 filed in 27 states in the United States relating to patients with IAs. One hundred fifty-nine practice claims between 2000 and 2020 filed in 27 states in the United States relating to patients with IAs. One hundred fifty-nine practice claims between 2000 and 2020 filed in 27 states in the United States relating to patients with IAs. One hundred fifty-nine practice claims between 2000 and 2020 filed in 27 states in the United States relating to patients with IAs. One hundred fifty-nine practice claims between 2000 and 2020 filed in 27 states in the United States relating to patients with IAs. 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One hundred fifty-nine practice claims between 2000 and 2020 filed in 27 states in the United States relating to patients with IAs. One hundred fifty-nine practice claims between 2000 and 2020 filed in 27 states in the United States relating to patients with IAs. Of the 17 cases in the failure to correctly interpret the CT or MR imaging category, 6 went to trial and only 2 resulted in judgments in favor of the plaintiff. In 1 case of blunt head trauma presenting as headache, findings of MR imaging of the brain were normal, but a subsequent CT showed SAH from a ruptured aneurysm. In this case, the plaintiff was awarded $43,000,000. The second case presented with syncope and severe headache in which CT of the head was read as an “unremarkable study.” The patient was discharged and had worsening symptoms but did not have further imaging until 2 weeks later when a CT showed a large intracranial bleed. The plaintiff was awarded $4,000,000.

**Limitations**

Various factors influence a plaintiff’s decision to file a claim, including the relationship with the physician and/or hospital or perceived financial incentives, which may influence cases going to trial but cannot be assessed in this analysis.

The legal databases used in the study do not contain a comprehensive list of all litigation filed across the United States. Cases that are resolved privately in the prelitigation setting before reaching trial would not be included in these data sets. Previous studies have reported that up to 85% of malpractice cases may be dropped, dismissed, or settled before trial. The available content varies by jurisdiction; some jurisdictions are more robust in sharing litigation materials with legal databases than others. However, these legal data sets are frequently used as a representation of legal precedent in outcome and value.

Case details within the database were not consistently clearly presented, making it difficult to accurately characterize some cases. There were multiple cases in which there were claims made against >1 party. There were also a handful of cases in which the method of resolution was mixed; ie, one party went to trial while another claim was dismissed. In such cases, the case was counted as 1 trial. A number of trials and settlements reported an undisclosed award amount, making it difficult to find accurate associations between award amounts and types of malpractice claims.

**CONCLUSIONS**

A review of the malpractice lawsuits in 2 major legal databases suggests a failure to clinically consider IA or do adequate imaging/work-up and failure to treat as the most frequent cause of action. Failure to correctly interpret imaging studies was a less frequent claim but may lead to significant financial liability. Although detection and treatment of IAs have increased in the past 2 decades, we did not see a corresponding increase in the frequency of lawsuits.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

**REFERENCES**

Aneurysm Treatment with Woven EndoBridge-17: Angiographic and Clinical Results at 12 Months from a Retrospective, 2-Center Series


BACKGROUND AND PURPOSE: This retrospective, 2-center study investigated the feasibility, safety, and efficacy at 12-month follow-up of the treatment of ruptured, unruptured, and recurrent intracranial aneurysms using the latest generation of the Woven EndoBridge (WEB) device, the WEB-17 system.

MATERIALS AND METHODS: Aneurysms treated with WEB-17 were extracted from the databases of 2 neurovascular centers. Patients, aneurysm characteristics, complications, and clinical and anatomic results were analyzed.

RESULTS: From February 2017 to May 2021, two hundred twelve patients with 233 aneurysms (181/233, 77.7%; unruptured-recurrent, and 52/233, 22.3%, ruptured) were included. High treatment feasibility (95.3%) was reported and was similar in ruptured aneurysms (94.2%) and unruptured-recurrent aneurysms (95.6%) ($P = .71$) and in typical (95.4%) and atypical (94.7%) locations ($P = .70$), but it was lower in aneurysms with an angle between the parent artery and main aneurysm axis of $\geq 45^\circ$ (90.2%) compared with those with an angle of $< 45^\circ$ (97.3%) ($P = .03$). Global mortality and morbidity were 1.9% and 3.8% at 1 month, respectively, and 4.4% and 1.9% at 12 months, respectively. One-month morbidity ($P = .02$) and mortality ($P = .003$) were higher in the ruptured group (10.0% and 8.0%, respectively) compared with unruptured-recurrent group (1.9% and 0.0%, respectively). Overall adequate occlusion (complete occlusion and neck remnant) was 86.3%. The percentage of adequate occlusion was higher ($P = .05$) in the unruptured-recurrent group (88.5%) compared with the ruptured group (77.5%).

CONCLUSIONS: The WEB-17 system showed high feasibility for ruptured and unruptured aneurysms, typical and atypical locations, and some aneurysms with an angle of $\geq 45^\circ$. As the most recent generation device, the WEB-17 also demonstrates high safety and good efficacy.


During the past 10 years, the intrasaccular Woven EndoBridge (WEB; MicroVention) device has completely changed endovascular treatment (EVT) of wide-neck intracranial aneurysms (IAs). After its introduction in Europe for clinical use,1 the WEB device evolved from the initial dual-layer (DL) version (WEB-DL) to the 2 single-layer (SL) versions (WEB-SL and WEB-SLS [single layer spherical]) and finally the enhanced visualization version that introduced drawn filled tubing technology to improve device fluoroscopy visibility.2 In parallel, WEB-specific microcatheters (VIA microcatheters; Sequent Medical) were designed to facilitate WEB deployment (VIA -33, VIA -27, and VIA -21). The most recent advance of the WEB device is the 17 system that permits delivery of small WEB devices (width = $\leq 7$ mm) through a 0.017-inch microcatheter. Additional WEB sizes have also been introduced, including a small device (width = 3 mm), half sizes (widths = 3.5 and 4.5 mm), and shalow devices with a 2-mm height.

The WEB was initially developed to treat wide-neck bifurcation aneurysms, specifically located at the MCA bifurcation, basilar artery tip, ICA terminus, and anterior communicating artery.

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Because the device is strictly endosaccular, there is no need for dual-antiplatelet treatment after WEB treatment, making it possible to treat unruptured and recurrent aneurysms as well as ruptured aneurysms.11-20

The Clinical Assessment of the WEB Device in the Ruptured Aneurysms (CLARYS) study recently confirmed the effectiveness of the WEB device in preventing aneurysm re-rupture in ruptured aneurysms.16 In parallel to the technical evolution of the WEB device, its indications progressively enlarged to distal and sidewall aneurysms.11-13

Several multicenter prospective series, including WEB Clinical Assessment of Intrasaccular Aneurysm Therapy (WEBCAST),3 WEBCAST 2,5 French Observatory,6 WEB Intrasaccular Therapy (WEB-IT),10 and CLARYS,21 have demonstrated favorable safety and efficacy of EVT with the WEB device; however, these studies were conducted before the introduction of the 17 system.

Given the limited data available regarding the safety and efficacy of the WEB-17 device,14,22-27 this retrospective 2-center study aimed to evaluate the feasibility, safety, and efficacy of mid-term follow-up (12 months) after the treatment of ruptured, unruptured, and recurrent IAs using WEB-17 system.

MATERIALS AND METHODS
Study Design
This retrospective, observational study included patients from 2 French neurovascular centers (Centre Hospitalier Universitaire, Reims and NEURI brain Vascular Center, Le Kremlin-Bicêtre). Both centers maintain an institutional prospective database that includes all patients treated with EVT for IA. From these databases, all patients treated with the WEB-17 until May 2021 were enrolled in the study.

The Comité d’Ethique pour la Recherche en Imagerie Médicale of Collège des Enseignants de Radiologie de France approved this retrospective study and waived written informed consent due to the retrospective study design (Institutional Review Board No. CRM-2207-293).

WEB Device
The WEB device consists of self-expanding, retrievable, electrothermally detachable, intrasaccular implants developed for the treatment of wide-neck bifurcation aneurysms.1,10,22-25,27 The WEB-17 is available in 2 configurations: WEB-SL (size range, 3 × 2 to 7 × 4 mm) and a more spherical WEB-SLS (size range, 4–7mm).27 The WEB-17 system debuted in Europe in December 201622 and is available in a small size (3 × 2 mm), in half sizes for the smallest size (with widths of 3.5 and 4.5 mm), and for shallow devices (with a 2-mm height for devices with a width between 3 and 5 mm). It is compatible with a straight or preshaped 0.017-inch microcatheter (VIA-17).25

Procedure
In the 2 centers, the decision for EVT was reached by consensus with neurosurgeons and neuroradiologists. Pre-, intra-, and postoperative antiplatelet therapy was similar in the 2 centers. For unruptured and recurrent aneurysms, dual-antiplatelet treatment with 75 or 160 mg of aspirin and 180 mg of ticagrelor per day was given 1 or 2 days preprocedure; if no stent was placed, ticagrelor was discontinued after the intervention and aspirin was maintained for 1 month. For ruptured aneurysms, aspirin, 250 mg IV, was administered during the procedure followed by oral aspirin for 1 month.

All procedures were performed on a biplane angiographic system (AlluraClarity; Philips Healthcare) with the patient under general anesthesia and systemic heparinization with triaxial access. The distal tip of VIA-17 microcatheter was always shaped with steam. The WEB size was selected according to measurements performed on 3D DSA: The WEB is typically oversized by 1 mm in width and undersized in height by 1 mm.

Follow-up
Follow-up was similar in both centers with 3- to 6-month and 12- to 18-month clinical and anatomic follow-up.

Data Collection
The following data were collected for each patient:
- Demographics: age and sex
- Aneurysm: location, status (ruptured, unruptured, and recurrent), and size (mean width, maximal width, maximal height, and maximal neck size); dome-to-neck ratio; angle between parent artery and main aneurysm axis
- Procedure: date, type (SL/SLS), and dimension of WEB used; additional device used; intra- and postprocedural complications;
- Retreatment of target aneurysm before the 12-month follow-up
- Angiographic and clinical follow-up at 12 months.

Data Analysis
Data analysis was performed by an interventional neuroradiologist (P.P.) independently of the procedures and clinical evaluations.

According to the initial WEB treatment indications, aneurysm location was classified into 2 groups:
- Typical location: AcomA, MCA bifurcation, ICA terminus, and basilar tip
- Atypical location: other ICA locations (ophthalmic, posterior communicating artery, anterior choroidal artery [AchoA]), A1-A2 segment, anterior-inferior cerebellar artery, posterior-inferior cerebellar artery, and superior cerebellar artery.

Aneurysms were dichotomized as wide-neck (neck of ≥ 4mm or dome-to-neck ratio of <2) and narrow-neck. Aneurysms were also classified in 2 groups according to the angle (α) between the parent artery and the neck-to-fundus axis (α < 45° and α ≥ 45°). The α was measured with 3D-DSA images.

For patients with ruptured aneurysms, the World Federation of Neurosurgical Societies (WFNS) grade before aneurysm treatment was collected. For all patients, pre- and postoperative clinical status was evaluated using the mRS. In patients with SAH, the mRS was evaluated on the basis of patient, family, or caregiver reports.

All complications were reviewed and classified into 4 categories: intraprocedural thromboembolic, intraprocedural hemorhagic, site of puncture, and postoperative (postprocedure and before 1 month). Complications were classified into 4 groups: no
symptoms, transitory deficit (when the duration of symptoms was <7 days), permanent deficit (when the duration of symptoms was ≥7 days), and death.

Morbidity was defined as mRS > 2 when the preoperative mRS was ≤2 and as an increase of 1 point when the preoperative mRS was >2. Morbidity and mortality were classified as procedure-related (related to all steps and all devices used during the procedure, including the WEB), SAH-related, and related to another disease.

Feasibility was evaluated in the global population and in relation to aneurysm status, to α (α < 45° and α ≥ 45°), and to location (typical and atypical). Aneurysm occlusion was evaluated with 12-month DSA using a 3-point scale: complete aneurysm occlusion, neck remnant, and aneurysm remnant. Clinical and angiographic results were evaluated in the global population and in 2 subgroups: unruptured-recurrent and ruptured aneurysms.

**Statistical Analysis**
Distribution normality was assessed using the Shapiro-Wilk test. Continuous variables were described as mean (SD) or median and interquartile range and were compared using the Student t test or Mann-Whitney U test. Categorical variables were presented as counts and compared using the χ² or Fisher exact test. ORs and their 95% CIs were calculated. A P value < .05 was considered statistically significant. Analyses were performed using MedCalc for Windows (Release 18.2; MedCalc Software).

**RESULTS**

**Patients and Aneurysms**
From February 2017 to May 2021, two hundred sixty patients with 281 aneurysms were treated with the WEB. During 224 procedures, 212/260 (81.5%) patients with 233/281 (82.9%) aneurysms were treated with the WEB-17, of whom 133/212 (62.7%) were women (Online Supplemental Data). The mean age was 55.2 (SD, 11.4) years. In 50/212 (23.6%) patients, 52/233 (22.3%) aneurysms were ruptured (WFNS score I for 25 patients, II for 12 patients, III for 4 patients, IV for 5 patients, and V for 4 patients). Three of 233 aneurysms (1.3%) were recurrent. Due to the small number, recurrent aneurysms were analyzed with the unruptured group.

**Treatment Feasibility**
The WEB was successfully implanted in 222/233 (95.3%) aneurysms, including 173/181 (95.6%) unruptured-recurrent and 49/52 (94.2%) ruptured (P = .71) aneurysms. Aneurysms were treated with the WEB-SL (188/222, 84.7%) or WEB-SLS (34/222, 15.3%). Feasibility was higher in the α < 45° group (167/172, 97.1%) compared with the α ≥ 45° group (55/61, 90.2%) (P = .03) but was similar for aneurysms in typical locations (186/195, 95.4%) and atypical locations (36/38, 94.7%) (P = .70). Adjunctive devices (including balloons) were used in 42/222 (18.9%) aneurysms (Table). A remodeling balloon, with or without an implantable device (flow diverter [FD], stent, or coils) was inflated in 25/220 (11.4%) WEB aneurysm treatments: 6/220 (2.7%) in aneurysms with α ≥ 45° and 3/220 (1.3%) in atypical locations. A stent or FD, with or without a balloon, was used in 19/222 (8.5%) procedures, all of them for unruptured-recurrent aneurysms (19/173, 10.9%). In 4/222 (1.8%) procedures, the WEB aneurysm treatment was performed with coils (2/173, 1.2%, unruptured-recurrent, and 2/49, 4.1%, ruptured), and in 1 procedure (1/222, 0.5%) using the WEB, coils and balloon were used to treat a ruptured aneurysm (1/49, 2.0%).

Treatment failed in 11/233 (4.7%) aneurysms (8/181 unruptured-recurrent, 4.4%; 3/52 ruptured, 5.8%): in 2 cases, the smallest WEB (WEB-SL, 3 × 2 mm) was too large; in 1 recurrent aneurysm initially treated with coiling, the WEB-SL was unstable in the aneurysm sac; in 8 procedures, 2 different WEB devices were deployed but did not adequately close the neck.

Complications were encountered in 2 of these 11 failed WEB treatments: In 1 patient treated with balloon-assisted coiling (BAC) for an unruptured AcomA aneurysm, perforation occurred during aneurysm coiling, leading to a small SAH without clinical worsening (mRS 0 at discharge); in the second situation 7 days posttreatment of an MCA bifurcation aneurysm with an FD, the patient experienced intrastent thrombosis with clinical worsening (the mRS at discharge and 12 months was 4).

**Complications and Morbidity-Mortality at 1 Month**
Complications are detailed in the Online Supplemental Data. Among 224 procedures, 15 (6.7%) thromboembolic inprocedureal events occurred. In 10 procedures, distal emboli were treated with intra-arterial administration of antiplatelet treatment (abicipimab or tirofiban) in 8 procedures and no additional treatment in 2 procedures. mRS at discharge was 0 in 6 patients, 1 in 3 patients, and 2 in 1 patient. Four patients treated for ruptured AcomA aneurysms had thrombosis of the pericallosal artery treated by intra-arterial administration of aspirin and/or tirofiban. In 2 patients, the clot was successfully dissolved, but the patients died due to SAH (WFNS = V and WFNS = IV). In 2 other patients, the clot was not dissolved and clinical evolution was deleterious (death at 45 days and mRS 4 at discharge and 12 months, respectively). Finally, 1 patient treated for an unruptured MCA aneurysm with the WEB and a stent had intrastent thrombosis successfully treated with intra-arterial tirofiban (mRS 1 at discharge).

A hemorrhagic inprocedureal complication occurred in 3/224 (1.3%) procedures. One patient treated with the WEB and a balloon for an unruptured A2 aneurysm experienced aneurysm rupture during balloon inflation (producing a large SAH leading to death 50 days later). In 1 patient treated for an unruptured AcomA aneurysm, WEB treatment failed and a minor hemorrhagic complication occurred during aneurysm coiling (see above). In a patient with an unruptured MCA aneurysm, a sac perforation occurred during catheterization with a microwire and was managed by WEB deployment. Postoperative CT showed limited SAH with slight clinical worsening (mRS 1 at discharge and 0 at 12 months).

In 2/224 (0.8%) procedures, there were complications at the puncture site, treated with surgery or endovascularly. In both cases, no clinical consequences at discharge were reported.

Postprocedureal complications were reported in 16/224 (7.1%) procedures. No delayed hemorrhagic complication (including bleeding/rebleeding of the aneurysm) was observed. Twelve patients experienced slight motor deficits a few days postprocedure with DWI- detected lesions in only 4 patients.
All 12 patients were treated medically (oral or IV antiplatelet medication) and had good clinical outcomes (mRS at discharge 0 in 10 patients and 1 in 2 patients). A patient treated for an ICA-AchoA unruptured aneurysm with the WEB only had an ischemic stroke 5 days postprocedure related to a WEB protrusion. One stent was placed in front of the neck during a second procedure, but intrastent thrombosis and a pericallosal embolic complication occurred and were unresolved at the procedure end despite the administration of an intra-arterial antiplatelet drug. The mRS at discharge and at 12 months was 4. Two patients experienced non-neurologic complications: pneumonia and acute lower limb ischemia in 1 patient (mRS at discharge, stable compared with preoperative status) and pneumonia in 1 patient (mRS at discharge was 2, and it was 0 at 12 months).

In 1 case of WEB failure, one patient was treated with an FD but experienced an intrastent thrombosis 7 days after the treatment (see above).

Finally, 36/212 (16.9%) patients had intraprocedural or postprocedural complications: no symptoms in 10/212 (4.7%), transitory symptoms in 16/212 (7.5%), permanent deficit in 6/212 (2.8%), and death in 4/212 (1.8%). Two of these 4 patients died after 1 month and were not included in the mortality at 1 month but were included in the mortality at 12-month evaluation (both considered procedure-related deaths). The other 2 patients had a thromboembolic intraprocedural complication and died 2 days posttreatment due to the severity of SAH (WFNS = V and WFNS = IV); these deaths were considered SAH-related and were included in the mortality at 1-month evaluation.

The overall morbidity and mortality at 1 month were 8/212 (3.8%) and 4/212 (1.9%), respectively. Morbidity was higher in patients with ruptured aneurysms than in those with unruptured-recurrent aneurysms (5/50, 10.0%, versus 3/162, 1.9%, respectively) (P = .02). Morbidity was procedure-related in 5/212 (2.4%; 2 of them WEB-related, 2/212, 1.0%) and SAH-related in 3/212 (1.4%). Mortality was higher in patients with ruptured aneurysms than in those with unruptured or recurrent aneurysms (4/50, 8.0%, versus 0/162, 0.0%, respectively) (P = .003). Mortality was related to SAH in all patients.

### Angiographic and Clinical Results at 12 Months

The Figure illustrates the participant flow chart for safety and efficacy analysis. Among the baseline population of 212 patients and 233 aneurysms, 205 patients (96.7%) and 197 aneurysms (84.5%) had 12-month follow-up (mean for 12-month DSA, 12.6 [SD, 4.9] months).

### Safety at 12 Months.

The overall morbidity was 4/205 (1.9%), and no statistical difference was reported between the unruptured-recurrent group (2/156, 1.2%) and the ruptured group (2/49, 4.0%) (P = .24). Morbidity was procedure-related in 3/205 (1.4%; 1 was WEB-related, 1/205, 0.5%) and SAH-related in 1/205 (0.5%).

The overall mortality rate was 9/205 (4.4%) and was significantly higher in the ruptured group (7/49, 14.3%) compared with unruptured-recurrent group (2/156, 1.2%) (P = .0008). Mortality was procedure-related in 2/205 (1.0%; 1 was WEB-related, 1/205, 0.5%), SAH-related in 6/205 (2.9%), and due to unrelated disease in 1/205 (0.5%).

### Efficacy.

Complete occlusion was reported in 133/197 (67.5%) aneurysms; neck remnant, in 37/197 (18.8%); and aneurysm remnant, in 27/197 (13.7%). In the unruptured-recurrent group, 108/157 (68.8%), 31/157 (19.7%), and 18/157 (11.3%) aneurysms had complete occlusion, neck remnant, and aneurysm remnant, respectively, and in the ruptured group, they were 25/40 (62.5%), 6/40 (15.0%), and 9/40 (22.5%), respectively.

Adequate occlusion (complete occlusion and neck remnant) in the overall population was 170/197 (86.3%). The percentage of adequate occlusion was higher (P = .05) in the unruptured-recurrent group (139/157, 88.5%) versus the ruptured group (31/40, 77.5%).

There were 4/197 aneurysms (2.0%) retreated before 12 months: 2/157 (1.3%) in the unruptured-recurrent group and 2/40 (5.0%) in the ruptured group (P = .18). Two aneurysms were treated with an FD; 1, with coiling; and 1, with stent-assisted coiling. At the time of retreatment, occlusion status was aneurysm remnant in the 4 aneurysms. Retreatment took place 5.2, 6.0, 8.5, and 9.6 months after the initial WEB procedure.
DISCUSSION
This analysis of aneurysm treatment with the WEB-17 system shows its high feasibility (95.3%), with a complication rate of 16.9% (36/212 patients), most of them associated with no or transient clinical worsening. Global mortality and morbidity rates were 1.9% (4/212 patients) and 4.4% (9/205 patients) at 1 month, respectively, and 4.4% (9/205 patients) at 12 months, respectively. All deaths at 1 month were related to SAH, and most deaths (7/9, 77.8%) at 12 months were related to SAH or unrelated disease. Morbidity at 1 and 12 months was also partially related to SAH: in 3/8 patients (37.5%) at 1 month and 1/4 patients (25.0%) at 12 months. Aneurysm treatment with the WEB was associated with a high feasibility (95.3%) with similar results in ruptured aneurysms (94.2%), unruptured-recurrent aneurysms (95.6%) \((P = .71)\), and in typical (95.4%) and atypical (94.7%) locations \((P = .70)\). In contrast, feasibility was lower in aneurysms with an angle of \(\geq 45^\circ\) (90.2%) compared with those with an angle of \(< 45^\circ\) (97.1%) \((P = .03)\). These data must be carefully interpreted because they relate to indications for aneurysm treatment with the WEB in the 2 centers of these studies (see Limitations). Our findings show that the WEB-17 system permits treatment of atypical and typical locations in the same percentage of cases, whereas some aneurysms with an angle of \(\geq 45^\circ\) remain difficult or impossible to treat.

Among the 11 WEB-treated failures reported in this series, in 8 procedures, 2 different WEB devices were deployed but did not adequately close the neck; especially in 2 procedures, the WEB SL \(6 \times 3\) mm and WEB SL \(5 \times 2\) were too large or too small, while the unavailable WEB SL \(6 \times 2\) mm would have been useful. These situations showed that at the moment, in some aneurysms with limited height, treatment with the WEB device is not a good option. Anyway, as WEB indication for aneurysm treatment progressively increasing, our results could suggest the existence of limitation of WEB sizing, especially for height dimension and that shallow WEB device is a really necessity in the current clinical scenario.
In this series, adjunctive implants (stent, FD, or coils), with or without balloon inflation, were used in 19/222 (8.6%) aneurysm treatments. This rate is in line with the WEBCAST (8.3%) and the French Observatory (11.3%) studies but higher compared with WEBCAST 2 (1.9%).

The rate of procedural and postprocedural complications was 16.9%; however, a permanent deficit was observed in only 6/212 (2.8%) patients, and 2 of these 6 patients had non-neurologic complications.

The percentage of thromboembolic complications was lower (7.1%) compared with what has been reported in the European Good Clinical Practice series (14.4%) or WEB-IT (10.0%). Several factors may explain this difference: 1) The European and US series were conducted at the beginning of clinical experience with the WEB; 2) the patients included in this series had the most recent WEB generation, while the patients in the European Good Clinical Practice studies were treated with the first WEB generation (WEB-DL) and second generation (WEB-SL and SLS); 3) antiplatelet protocols have evolved, and not all patients were premedicated with dual-antiplatelet treatment in the European and US series; 4) the microcatheter used in this series has the smallest size (VIA-17) compared with microcatheters used in the European and US series (including VIA-33, VIA-27, and VIA-21); and 5) most aneurysms included in this series were small.

Other recent retrospective series showing the results of aneurysm treatment with the WEB-17 device reported a rate of thromboembolic complications similar to ours: in van Rooij et al.,22 5.0%; in Pagano et al.,23 5.5%; in Maurer et al.,22 4.2%; in König et al.,26 5.7%; in Mihalea et al.,24 4.0%; in Goertz et al.,27 5.3%; and in Zimmer et al.,14 6.4.

In contrast to thromboembolic complications, the rate of procedural hemorrhagic complications was similar in this series (1.4%), the European series (1.2%), and WEB-IT (1.3%). Since beginning of clinical practice with WEB, it has been clearly shown that the rate of intraoperative rupture is very low. In the present series, only 1 patient died (50 days after the procedure) due to an intraprocedural rupture, related to balloon use and not to the WEB device.

The rate of delayed complications was not low (7.5%). None were hemorrhagic, and a few were infectious (2/16 patients). Most delayed complications were likely ischemic or hemodynamic, were treated with antiplatelet medication, and had good clinical outcome.

Anatomic results in this series were slightly better compared with previous series. The rate of complete aneurysm occlusion at 12 months was 67.5% compared with 52.9% in the European studies and 53.8% in WEB-IT. However, the rate of adequate occlusion was only slightly superior in the present series (86.3%) compared with European studies (79.1%) and WEB-IT (84.6%). These results are probably explained by the factors noted above regarding thromboembolic complications.

In this series, feasibility was similar in ruptured aneurysms (94.2%) and unruptured-recurrent aneurysms (95.6%) (P = .71). The complication rate was also similar in both groups (20.0% in ruptured and 16.0% in unruptured-recurrent aneurysm) (P = .52). Of note, the rate of intraprocedural thromboembolic complications was significantly higher in ruptured (18.0%) than in unruptured aneurysms (3.7%) (P = .001). Moreover, due to SAHs in all cases, mortality at 1 month was significantly higher in ruptured aneurysms (8.0%) compared with unruptured-recurrent (0.0%) (P = .003) aneurysms. Morbidity was also higher in the ruptured group (10.0%) compared with the unruptured-recurrent group (1.9%) (P = .02). Finally, anatomic results were not significantly different, but adequate occlusion was more frequent in unruptured-recurrent aneurysms (88.5%) compared with ruptured aneurysms (77.5%) (P = .05).

In the CLARYS study,21 12-month anatomic results were slightly different compared with the present series, with a lower rate of complete aneurysm occlusion (41.3%) and higher rates of neck (45.7%) and aneurysm (13.0%) remnants. However, the rate of adequate occlusion was higher (87.0%). Because all aneurysms were treated with the WEB-21 system in the CLARYS study, it is likely that the characteristics of the WEB-17 system (smaller system profile, half sizes, shallow devices) were responsible for the higher rate of complete aneurysm occlusion.

The rate of aneurysm retreatment at 12 months was globally low (4/197, 2.0%). The rate of retreatment was statistically not different between the unruptured-recurrent (2/157, 1.3%) and the ruptured (2/40, 5.0%) (P = .18) groups.

**Limitations**

This study has several limitations. First, our results are based on a retrospective analysis. This limitation is partially mitigated by all patients treated with WEB-17 being prospectively included in the database from 2 neurovascular centers. Second, the feasibility of WEB-17 aneurysm treatment was evaluated on the basis of the initial indication for WEB aneurysm treatment by the teams. Some aneurysms were likely not treated with the WEB on the basis of the team’s decisions due to anticipated treatment complexity. These decisions could potentially have biased some results regarding feasibility.

**CONCLUSIONS**

The most recent generation of the WEB device (WEB-17 system) is associated with high feasibility of the treatment (95.3%), high safety (with 1-month morbidity and mortality 3.8% and 1.9%, respectively), and good efficacy (12-month adequate occlusion in 86.3%). Moreover, our findings indicate similar feasibility in unruptured-recurrent (95.6%) and ruptured (94.2%) aneurysms and in typical (95.4%) and atypical locations (94.7%); however, feasibility is slightly lower in aneurysms with an angle of ≥45° (90.2%) compared with aneurysms with an angle of <45° (97.1%). Ruptured aneurysms are associated with higher morbidity and mortality rates (4.0% and 14.3%, respectively), mostly due to the consequences of SAH. Finally, 12-month adequate occlusion was more frequent in the unruptured-recurrent group (88.5%) compared with the ruptured group (77.5%).

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org

**REFERENCES**


The FRESH Study: Treatment of Intracranial Aneurysms with the New FRED X Flow Diverter with Antithrombotic Surface Treatment Technology—First Multicenter Experience in 161 Patients


ABSTRACT

BACKGROUND AND PURPOSE: Flow diverters with antithrombotic coatings are increasingly used to improve the safety of flow diverter treatments of intracranial aneurysms. This study aimed to investigate the safety and short-term efficacy of the new FRED X flow diverter.

MATERIALS AND METHODS: Medical charts and procedural and imaging data of a consecutive series of patients with intracranial aneurysms who were treated with the FRED X at 9 international neurovascular centers were retrospectively analyzed.

RESULTS: One hundred sixty-one patients (77.6% women; mean age, 55 years) with 184 aneurysms (11.2% acutely ruptured) were included in this study. Most aneurysms were located in the anterior circulation (77.0%), most frequently at the ICA (72.7%). The FRED X was successfully implanted in all procedures. Additional coiling was performed in 29.8%. In-stent balloon angioplasty was necessary in 2.5%. The rate of major adverse events was 3.1%. Thrombotic events occurred in 7 patients (4.3%) with 4 intra- and 4 postprocedural in-stent thromboses, respectively (1 patient had both peri- and postprocedural thrombosis). Of these thrombotic events, only 2 (1.2%) led to major adverse events (ischemic strokes). Postinterventional neurologic morbidity and mortality were observed in 1.9% and 12%, respectively. The rate of complete aneurysm occlusion after a mean follow-up of 7.0 months was 66.0%.

CONCLUSIONS: The new FRED X is a safe and feasible device for aneurysm treatment. In this retrospective multicenter study, the rate of thrombotic complications was low, and the short-term occlusion rates are satisfactory.

ABBREVIATIONS: ASA = acetylsalicylic acid; BA = basilar artery; FD = flow diverter; HH = Hunt and Hess; OKM = O’Kelly-Marotta; PcomA = posterior communicating artery; RROC = Raymond-Roy occlusion classification

The treatment of intracranial aneurysms with flow diverters (FDs) has emerged as an established treatment option for a considerable number of aneurysms.1-4 The functional principle of FDs is based on a dense mesh of stent struts, which diverts the flow within the target vessel past the aneurysm, eventually leading to the occlusion of the aneurysm. This relatively high metal coverage of the vessel wall, which is higher compared with conventional intracranial stents, can trigger thrombosis within the FD, which is a feared complication during and after FD treatments because it can lead to distal emboli and stent occlusion, eventually causing ischemic stroke.5,6 An emerging trend in the field of FD treatment of intracranial aneurysms is the use of FDs with specific antithrombotic coatings, which aim to reduce the risk of this potentially harmful complication.7,8 The Flow-Redirection Intraluminal Device (FRED; MicroVention) is one of the most frequently used FDs worldwide. Its safety and efficacy were demonstrated in numerous studies during the past years.9-11 After the publication of the FRED pivotal trial, it received FDA approval in the United States in 2020.12 The FRED X, which was introduced only recently, is a new version of the FRED. The novelty of this successor product is the X-technology, a specific antithrombotic surface treatment that is applied to the stent.

The aim of this multicenter study was to investigate the peri- and postprocedural safety and the short-term efficacy of the...
new FRED X FD for the treatment of ruptured and unruptured intracranial aneurysms. The participating centers received the FRED X as part of a limited market release.

**MATERIALS AND METHODS**

**Study Design**
The FRESH study - Treatment of Intracranial Aneurysms with the New FRED X Flow Diverter with Anti-thrombotic Surface Treatment Technology - is a retrospective, multicentric, observational study at 9 international high-volume neurovascular centers. A survey, which was specifically designed for this study, was completed by the physicians who performed the treatments with the FRED X. On the basis of these surveys, the clinical, radiologic, and procedural parameters of patients with ruptured and unruptured intracranial aneurysms who were treated with the FRED X between January 2020 and March 2022 were systematically analyzed. The observation period, including the assessment of postprocedural events and the degree of occlusion at the latest imaging, was from January 2020 until June 2022. A part of this patient cohort was also included in the FRED/FRED Jr/FRED X Intracranial Aneurysm Treatment Study (FRITS; not yet published, ClinicalTrials.gov Identifier: NCT03920358). The institutional ethics committees approved this study.

**Patient Data**
The patient data included age, sex, and the initial clinical presentation. The pre- and posttreatment clinical statuses of the patients were assessed using the mRS. For patients with an acutely ruptured aneurysm, the clinical status was assessed according to the Hunt and Hess (HH) scale.

**Aneurysm Data**
The assessed characteristics of the treated aneurysms included the location of the aneurysm, the aneurysm type (saccular, fusiform, blister-like, or dissecting), the size of the aneurysm (maximal diameter), and the diameter of its neck. The diameter of the parent vessel proximal and distal to the aneurysm was also assessed. Wide-neck aneurysms were defined as those with a neck diameter of ≥4 mm or aneurysms with a dome-to-neck ratio of <2.

**FRED X: Device Characteristics**
As mentioned in the beginning of the article, the novelty of the FRED X is a specific anti-thrombotic surface treatment. The X-technology, which is applied to the new FRED X device, is based on the material poly-2-methoxyethyl acrylate. The nanopolymer surface treatment is derived from the Xcoating surface treatment (Terumo), which has also been applied in other cardiovascular devices, such as oxygenators and arterial filter lines for >30 years. The surface treatment comprises an amphiphilic polymer with a hydrophobic part toward the device and a hydrophilic part toward the vessel lumen (and blood) or vessel wall, leading to a boundary layer adjacent to the stent struts, which aims to reduce protein denaturation and thus platelet adhesion. Apart from the X-technology surface treatment, the FRED X is identical to the FRED and FRED Jr with its specific dual-layer design, comprising a low-porosity inner mesh and a high-porosity outer stent. However, there was a change in the designation of the devices. For its precursor, the larger devices with a diameter of ≥3.5 mm, which featured a distal tip and had to be delivered with a 0.027-inch microcatheter, were named “FRED,” and the smaller devices with a diameter of ≤3.0 mm, which did not have a distal tip and could be delivered with a 0.021-inch microcatheter, were named “FRED Jr.” In contrast, all sizes of the new device are named FRED X, while the design of the larger (≥3.5 mm) and smaller (≤3.0) devices (distal tip, microcatheter compatibility) remained unchanged.

**Procedural Parameters**
The assessed procedural parameters included the peri-interventional antithrombotic medication, as well as treatment characteristics, such as the procedure duration, the number of implanted devices, additional coiling, and the need for in-stent balloon angioplasty.

Ease of deployment, vessel wall apposition, and radiopacity of the device were rated overall by the treating interventionalist for each treatment, using a 5-point scale (1, very poor; 2, poor; 3, intermediate; 4, good; 5, very good). Additionally, the general performance of the FRED X was compared with its precursor, FRED/FRED Jr, also using a 5-point scale (1, worse; 2, slightly worse; 3, equivalent; 4, slightly better; 5, better) for each treatment.

Periprocedural technical difficulties as well as peri- and postinterventional adverse events were assessed. The severity of adverse events was defined as described previously. A minor adverse event was defined as an event that resolved within 7 days without any clinical sequelae, while a major adverse event was defined as an ongoing clinical deficit at 7 days following the event. Clinical evaluation was performed before the procedure, immediately after the procedure, 24 (±6) hours after the procedure, at discharge, and at follow-up visits.

**Follow-up**
Clinical and imaging follow-up was performed according to the individual protocol of the respective centers. At the follow-up visits, the clinical condition of the patients was assessed, and imaging was performed. In follow-up imaging, the degree of in-stent stenosis was assessed and categorized as “not present,” “mild” (defined as ≤50% stenosis, compared with the immediate postinterventional diameter), “moderate” (50%–75%), “severe” (>75%), or “complete occlusion.”

**Assessment of the Degree of Occlusion**
The grade of aneurysm occlusion immediately after the procedure was reported according to the O’Kelly-Marotta (OKM) scale. Because invasive angiography was not available for all follow-ups, the grade of occlusion at the latest follow-up was reported according to the Raymond-Roy occlusion classification (RROC) for all patients. Adequate occlusion was defined as complete occlusion or residual neck (OKM C and D and RROC I and II).

**RESULTS**
One hundred sixty-one consecutive patients with 184 aneurysms treated with the FRED X device were included in this study. Patient and aneurysm characteristics are summarized in Table 1.
Results subdivided into unruptured and ruptured aneurysms are summarized in the Online Supplemental Data.

### Patient Characteristics

The mean age of the patients was 55.1 years, and 77.6% were women. The median pretreatment mRS was 0 (first quartile; third quartile, 0; 0) (mRS 0 in 126 patients [78.3%], mRS 1 in 24 [14.9%], and mRS 4 in 1 [0.6%]). The patient with mRS 4 presented with a subacute brainstem infarction caused by a large, fusiform, unruptured aneurysm of the basilar artery (BA). Of the 18 patients (11.2%) who presented with an acutely ruptured aneurysm, the HH scale was 1 (first quartile; third quartile, 1; 2.5) (HH 1 in 8 patients [53.3%], HH 2 in 3 patients [20.0%], HH 3 in 2 patients [13.3%], and HH 5 in 2 patients [13.3%]). In 100 patients (62.1%), the aneurysm was incidental and asymptomatic.

### Aneurysm Characteristics

Most patients (89.4%) had only 1 aneurysm treated with the FRED X, while in 8.1%, 2 aneurysms, and in 1.2%, 3 aneurysms were treated. The most frequent aneurysm location was the ICA (72.7%), followed by the BA (8.1%) and the MCA (6.2%). The mean aneurysm size was 7.8 mm, ranging from 1-mm blister-like to 46-mm giant aneurysms. Most aneurysms had a wide neck (90.1%), a saccular shape (81.4%), and were sidewall aneurysms (84.5%).

### Antiplatelet Therapy

Pre-, intra-, and postprocedural platelet inhibition and testing of the thrombocyte aggregation response were managed according to local standards of the respective institutions. Platelet reactivity testing was performed in 91.9% of the patients. The most common antiplatelet medications were acetylsalicylic acid (ASA) plus clopidogrel (62.4%), ASA plus prasugrel (21.0%), and ASA plus ticagrelor (6.4%). Patients with acute aneurysmal SAH received periprocedural tirofiban, followed by double-antiplatelet therapy after the treatment.

### Treatment

The treatment characteristics are summarized in Table 2 and the Online Supplemental Data. Two example cases are illustrated in Figs 1 and 2.

---

**Table 1: Patient and aneurysm characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Incidental</th>
<th>Regrowth/persistent aneurysm</th>
<th>SAH</th>
<th>Headache</th>
<th>Co- incidental</th>
<th>Diplopia</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (mean) (yr)</td>
<td>55 (SD, 12)</td>
<td>27–79</td>
<td></td>
<td>9 (5.6%)</td>
<td>6 (3.7%)</td>
<td>3 (1.9%)</td>
<td>5 (3.1%)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>100 (62.1%)</td>
<td>12 (4.4%)</td>
<td>18</td>
<td>(11.2%)</td>
<td>9 (5.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm location</td>
<td>ICA 117</td>
<td>BA 13</td>
<td>MCA</td>
<td>10 (6.2%)</td>
<td>VA 9 (5.6%)</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Aneurysm size (mean) (range)</td>
<td>7.8 (SD, 6.3)</td>
<td>4.7 (SD, 3.8)</td>
<td>1.7 (SD, 0.9)</td>
<td>1 (0.4–7.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck diameter (mean) (range)</td>
<td>Proximal 3.5 (SD, 0.8)</td>
<td>Distal</td>
<td>3.1 (SD, 0.7)</td>
<td>1.2–5.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of the parent artery proximal and distal to the aneurysm mean (range)</td>
<td>1 (5.7–7.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm type</td>
<td>Saccular 131 (81.4%)</td>
<td>Blister-like 14 (8.7%)</td>
<td>Fusiform 11 (6.8%)</td>
<td>Dissecting 5 (3.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sidewall or bifurcation aneurysm</td>
<td>Sidewall 136 (84.5%)</td>
<td>Bifurcation 25 (15.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Treatment parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysms treated in the respective treatment session</td>
<td>144 (89.4%)</td>
<td>13 (8.1%)</td>
<td>2 (1.2%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Ease of deployment</td>
<td>Very poor</td>
<td>Poor</td>
<td>Intermediate</td>
<td>Good</td>
</tr>
<tr>
<td>Vessel wall apposition</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>12 (7.5%)</td>
</tr>
<tr>
<td>Radiopacity</td>
<td>Very poor</td>
<td>Poor</td>
<td>Intermediate</td>
<td>Good</td>
</tr>
<tr>
<td>Performance compared with FRED/FRED Jr</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>59 (36.7%)</td>
</tr>
<tr>
<td>Additional coiling</td>
<td>Worse</td>
<td>Slightly worse</td>
<td>Equivalent</td>
<td>Slightly better</td>
</tr>
<tr>
<td>In-stent balloon angioplasty</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>154 (96.3%)</td>
<td>6 (3.8%)</td>
</tr>
</tbody>
</table>

**Table 2: Treatment parameters**

<table>
<thead>
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<th>Parameters</th>
<th>1</th>
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<tr>
<td>Radiopacity</td>
<td>Very poor</td>
</tr>
<tr>
<td>Performance compared with FRED/FRED Jr</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Additional coiling</td>
<td>48 (29.8%)</td>
</tr>
</tbody>
</table>
Table 3: Adverse events and complications

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Technical periprocedural adverse event</th>
<th>Minor adverse event</th>
<th>Major adverse event</th>
<th>Neurological morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (3.1%)</td>
<td>21 (13.0%)</td>
<td>5 (3.1%)</td>
<td>3 (1.9%)</td>
<td>2 (1.2%)</td>
</tr>
</tbody>
</table>

*Data are absolute number of cases (relative frequency in %).

Table 4: Occlusion rates

<table>
<thead>
<tr>
<th>Occlusion rates</th>
<th>I: Complete occlusion</th>
<th>II: Residual neck</th>
<th>III: Residual aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusion at latest follow-up</td>
<td>94 (66.2%)</td>
<td>24 (16.9%)</td>
<td>24 (16.9%)</td>
</tr>
</tbody>
</table>

*Data are absolute number of cases (relative frequency in %).

Imaging follow-up was available for 142/161 patients with a mean follow-up period of 7.0 months, reported according to the RROC.

One hundred sixty-seven FRED X devices were implanted in 161 treatment sessions (1 FD was implanted in 155 treatments, and 2 FDs in 6 treatments) with a mean duration of 80.2 [SD, 47.5] minutes. A FRED X FD could be successfully implanted as planned in all treatments. Recapturing or repositioning of the device was required in 14.3% of the treatments. Additional coiling of the aneurysm was performed in 29.8%. The reasons for additional coiling were large aneurysm size, irregular aneurysm shape, and aneurysmal hemorrhage. In-stent balloon angioplasty to improve the vessel wall apposition was performed in 2.5%.

The ease of deployment was rated "good" or "very good" in 98.8%. It was rated "poor" in 1 case (0.6%) in which the stent kinked at a sharp curve in the vessel. Vessel wall apposition was rated good or very good in 98.8%. Radiopacity was rated good or very good in all cases (100%). When we compared the FRED X with its precursor, it was rated "equivalent" in 96.3% and "slightly better" in 3.8%.

**Adverse Events and Complications**

Asymptomatic and symptomatic adverse events are presented in detail in the Online Supplemental Data and summarized in Table 3.

Intraprocedural technical adverse events occurred in 5 treatments (3.1%) and consisted of 2 cases of inadvertent stent shortening, as well as stent kinking, insufficient stent opening, and coil migration in 1 case, respectively. All of these adverse events were asymptomatic.

Most (95.8%) of recorded symptomatic adverse events occurred postinterventionally. Minor adverse events occurred in 13.0% of the patients. Nine of 21 of these events were neurologic, resulting in a minor neurologic adverse event rate of 5.6%. Major adverse events (2 ischemic strokes, 1 intracerebral hemorrhage, 1 mass effect of the aneurysm, and 1 case of vasospasms caused by a preinterventional aneurysmal SAH) were observed in 5 patients (3.1%), leading to neurologic morbidity in 3 (1.9%) and death in 2 patients (1.2%). All these major adverse events were neurologic complications.

One of the major adverse events was a major ischemic stroke, which occurred 2 weeks after an uneventful treatment of an unruptured posterior communicating artery (PcomA) aneurysm, due to severe in-stent thrombosis, leading to hemodynamic cerebral infarctions. This patient had a good response to ASA and clopidogrel in the reactivity testing before treatment. Treatment in this case was performed with tirofiban, which led to a resolution of the thrombus, followed by oral medication with ASA in combination with prasugrel. The patient was discharged with mRS 3 and recovered to mRS 2 at 6 months after treatment. The second patient who had neurologic morbidity presented with a large BA aneurysm causing brainstem infarctions, which increased after the FD treatment (worsening of pre-existing stroke), without any evidence of thrombus formation. Of the patients who died, 1 patient with an enlarging giant BA aneurysm died due to increasing mass effect despite the treatment. The second case of mortality occurred in a patient with aneurysmal SAH, who developed an intracerebral hemorrhage located adjacent to the external ventricular drainage. Consequently, tirofiban had to be stopped, which led to occlusion of the stent in the ICA, eventually leading to cerebral infarction and death.

Postinterventional visual disturbances occurred in 5 patients (3.1%). In all of these patients, an aneurysm of the ICA was treated with an FD, which covered the ophthalmic artery.

A total number of 8 thrombotic events was reported in 7 patients (4.3%). In 4 of these, slight in-stent thrombosis was observed during treatment, which was immediately treated with tirofiban, leading to complete resolution of the thrombus in all cases without any clinical sequelae. Postinterventional in-stent thrombosis occurred in 1 of the 4 patients with intraprocedural thrombosis (despite complete intraprocedural thrombus resolution after tirofiban administration and after discontinuation of ticagrelor intake by the patient) and in 3 further patients with an uneventful treatment procedure. One of these patients developed an asymptomatic stent occlusion. Another stent thrombosis occurred after stopping tirofiban due to an intracerebral hemorrhage as described above. Apart from this patient, only 1 thrombotic event resulted in a major adverse event: the case of a major stroke that is described in more detail above.

**Clinical Follow-up**

Two patients died during the follow-up (listed under adverse events and complications), resulting in a mortality rate of 1.2%. The mean mRS at the latest follow-up, which was available for 133 patients, was 0.4 (SD, 1.0) (mRS 0 in 102 patients [76.7%], mRS 1 in 18 [13.5%], mRS 2 in 8 [6.0%], mRS 3 in 4 [3.0%], and mRS 6 in 2 [1.5%]). Deterioration of the mRS (compared with the preinterventional scale) was observed in 11 patients; 4 deteriorations were related to the procedure or the underlying disease (see adverse events and complications). For the remaining patients, mRS deterioration was caused by non-neurologic conditions.
Imaging Follow-up

Imaging follow-up was available for 145 of the 161 patients (90.1%), with a mean imaging follow-up period of 7.0 (SD, 4.3) months. The patients without follow-up imaging refused further imaging, were lost to follow-up, or died.

The imaging technique was invasive conventional angiography and MR imaging in 22.1%, conventional angiography alone in 14.5%, MR imaging and flat panel CT in 28.3%, MR imaging only in 30.3%, and flat panel CT only in 4.8%.

During follow-up, in-stent stenosis or stent occlusion was observed in 17 patients (10.6%). Most of these cases (14/17, 82.4%) were only mild stenoses. There were 2 cases of moderate in-stent stenosis and 1 case of complete stent occlusion. Of all these cases, only 1 patient was symptomatic: the above-mentioned patient with major stroke due to in-stent thrombosis. The moderate in-stent stenosis persisted in the latest follow-up imaging.

Aneurysm Occlusion

The aneurysm occlusion rates are summarized in Table 4. The immediate postinterventional occlusion rates were as follows: OKM A1 in 19.9%, A2 in 23.0%, A3 in 20.5%, B1 in 2.5%, B2 in 5.6%, B3 in 13.7%, C1 in 1.2%, C2 in 5.0%, C3 in 4.4%, and D in 4.4%.

At the latest follow-up, aneurysm occlusion rates were as follows: RROC I in 66.2%, RROC II in 16.9% and RROC III in 16.9%, resulting in a rate of adequate aneurysm occlusion of 83.1%.

DISCUSSION

FDs have increasingly become a treatment option for cerebral aneurysms with the drawback of a higher metal density being potentially more thrombogenic than conventional stents. In this multicenter cohort, the first study reporting on the new FRED X with antithrombotic surface treatment, the FD showed a satisfactory safety profile and proved to be effective judged by short-term aneurysm occlusion.

As explained, the only modification of the FRED X toward its precursor is the new antithrombotic surface treatment. In this study, thrombotic complications occurred in 7 of 161 patients, resulting in a thrombotic complication rate of 4.3%, of which only 2 led to a major adverse event (one occurring after a necessary discontinuation of antiplatelet therapy because of an intracerebral hemorrhage). This low but still considerable number of thrombotic events indicates that even when using devices with antithrombotic coatings, high awareness is still mandatory for both peri- and postprocedural thromboses.

In recent studies on the FRED and FRED Jr, the rate of thrombotic complications was slightly higher. In the Safety and Efficacy Analysis of FRED Embolic Device in Aneurysm Treatment (SAFE) study, the pivotal study for the FRED in France (published in 2019),18 thromboembolic complications occurred in 7/103 patients (6.8%). In the US pivotal trial (2022), device thrombosis was reported in 12/145 patients (8.3%).19 These thrombotic events rates are also in line with reported data for other FDs, such as the Pipeline Embolization Device (PED; Medtronic). A meta-analysis, comprising data of 1110 patients, focusing on thrombotic complications after PED treatment reported an overall rate of 7.0% thrombotic events.20 The new antithrombotic surface treatment might serve as an explanation for the slightly lower thrombotic complication rate in this study. However, the FRESH study was based on a retrospective, self-adjudicated analysis, the cohort in our study was heterogeneous, and there was no control group consisting of patients treated with the precursor devices, preventing a direct comparison of these studies and the devices regarding thrombogenicity. Prospective trials are warranted to further assess the safety of the FRED X and its potential to reduce the rate of thrombotic complications compared with conventional FDs.

The nonthrombotic complications in this study (minor adverse events in 13.0% and major adverse events in 3.1%) are
similar to those reported in previous studies for the FRED and FRED Jr. In the largest study reporting on the FRED, the European Flow-Redirection Intraluminal Device Study, comprising data of 531 patients, the rate of complications and adverse events was 14%. In the above-mentioned US pivotal trial, the composite primary safety end point of major stroke or death within 30 days or major ipsilateral stroke or neurologic death after 30 days was met by 6.2% of the patients.

Because the FRED X is technically identical to the FRED and FRED Jr, despite the antithrombotic surface treatment, it is consistent that the occlusion rates in this study are similar to those reported for its precursor. The rate of complete occlusion at a mean follow-up of 7.0 months was 66.2% in our cohort. In the European Flow-Redirection Intraluminal Device Study, the complete occlusion rate was 82.5% at 6 months and 91.3% at 1 year. For the above-mentioned pivotal trials, the complete occlusion rate was 61.1% at 6 months and 73.3% at 1 year for the French study and 62.9% at 1 year for the US study. Occlusion rates of follow-up period in this study was relatively short, due to the novelty of the device.

CONCLUSIONS
The FRED X is a safe and feasible FD for treatment of ruptured and unruptured intracranial aneurysms. With its new antithrombotic surface treatment, the rate of thrombotic complications was relatively low, and the short-term efficacy is promising.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES
ABSTRACT
SUMMARY: Pedicled locoregional submandibular gland reconstruction flaps are increasingly used in oncologic head and neck surgery and have unique imaging characteristics that can mimic locally recurrent tumor. In this clinical report, 23 posttreatment imaging studies were evaluated in 19 patients who had undergone submandibular gland flap reconstructions after resection of a primary head and neck tumor. Submandibular gland flaps were most commonly mobilized into the parapharyngeal space or parotid bed, with others located inferior to the mandibular body and within marginal mandibulectomy defects. The original shape of the gland was typically not preserved. Identifying the submandibular gland hilum, vascular pedicle, glandular texture, and absence of submandibular gland in the orthotopic location was most useful in recognizing a flap. The interpreting radiologist must be familiar with the unique submandibular gland flap imaging characteristics to accurately differentiate normal postoperative appearance and recurrent tumor.

ABBREVIATIONS: SCC = squamous cell carcinoma; SMG = submandibular gland

Surgical flaps are commonly encountered during surveillance imaging following oncologic resection in the head and neck, particularly as advancements in microvascular surgical techniques have facilitated the widespread use of free flaps. The resultant complex postoperative anatomy can make imaging interpretation challenging. To aid the interpreting radiologist, multiple studies have characterized the typical postoperative imaging appearance of various fasciocutaneous and myocutaneous flap reconstructions in the head and neck.1-3 To our knowledge, existing studies have not characterized the imaging appearance of pedicled locoregional glandulofascial flaps involving the submandibular gland (SMG).

First described by Mozolewski et al4 for laryngeal reconstruction, the SMG flap has since been described for the reconstruction of small-to-medium defects that cannot be closed primarily yet may not necessitate the additional risk and surgical complexity of free flaps.5 From a surgical perspective, the benefits of a pedicled regional SMG flap include an abundant blood supply from the facial artery, the option to include surrounding adipose tissue for bulk, and a relatively long arc of rotation, thereby allowing mobilization to sites as far as the infratemporal fossa or parotid bed.6,7 Furthermore, in instances when level 1 nodes will be dissected, no additional incision or secondary surgical defect is required, unlike the temporalsis myofascial or pectoralis flaps.5-7 In comparison with myocutaneous flaps, an SMG flap retains greater bulk across time, therefore obviating surgical overestimation of tissue volume necessary to reconstruct a defect.6 This feature may more accurately restore a desired facial contour after parotidectomy or preserve mucosal volume of an oropharyngeal defect in which the swallowing function could be eventually impaired by flap atrophy. Of note, SMG transfer to the submental space with the intent of avoiding the high-dose radiation field to avoid xerostomia is a distinct entity and not included herein.8 A key difference between these entities is that SMG transfer is performed on the SMG contralateral to the site of disease, whereas SMG flap reconstruction is performed ipsilaterally.

As previously described in the literature, the postlaryngectomy imaging appearance of a mobilized thyroid gland can simulate recurrent tumor.9 Likewise, the postoperative appearance of an SMG flap reconstruction may consist of hyperattenuating, nodular tissue in the primary resection site, whereby an interpreting radiologist who is unfamiliar with this technique may easily mischaracterize normal flap reconstruction for recurrent tumor (Fig 1). The purpose of this study was to characterize the normal CT and MR imaging postoperative appearance of SMG flaps to avoid this pitfall in the posttreatment setting.

Case Series
In this institutional review board–exempt and Health Insurance Portability and Accountability Act–compliant study, we retrospectively reviewed the records of a tertiary oncologic otolaryngology...
surgical practice performing pedicled locoregional glandulofascial flap reconstruction during 2014–2022, yielding 37 patients. We excluded all patients with no postoperative imaging and any patients in whom glands other than the SMG were used for the flap reconstruction (eg, thyroid glands mobilized to bolster the pharyngeal closure following laryngectomy). Nineteen patients met the inclusion criteria. All patients underwent an SMG flap operation with the intent of reconstruction and not transfer of the gland to shield it from high-dose radiation (ie, Seikaly and Jha submandibular transfer procedure).8

In total, 23 studies of SMG flaps were characterized, including 16 CTs and 7 MR images. Preoperative imaging was available for 14 patients, consisting of 12 CTs and 3 MR images. All CTs were performed with IV iodinated contrast and included multiplanar reconstructions. Of these, CT examinations performed at our institution included administration of 100 mL of iopamidol (Isovue; Bracco) using a split bolus technique of 60 mL contrast at 2.5 mL/s, a 35-second pause, 40 mL of contrast at 2.5 mL/s, 40 mL of saline at 2.5 mL/s, and scanning at 90 seconds after start of the injection. All MR imaging was performed without and with IV gadolinium-based contrast and consisted of, at a minimum, T1-weighted, T2-weighted fat-suppressed, DWI, and T1-weighted fat-suppressed postcontrast sequences. Of these, MR imaging examinations performed at our institution included administration of gadobenate dimeglumine (MultiHance; Bracco) per weight-based dosing.

RESULTS

In 19 patients, SMG flaps were used for reconstruction following primary resection of squamous cell carcinoma (SCC) of the oral cavity (n = 7), SCC of the oropharynx (n = 3), poorly differentiated carcinoma of the parotid (n = 2), parapharyngeal synovial cell sarcoma (n = 2), 1 case of metastatic SCC of unknown primary (p16 negative), and individual cases of mandibular ameloblastoma, deep lobe parotid pleomorphic adenoma, parotid adenoid cystic carcinoma, and parotid salivary ductal carcinoma. The time between the operation and imaging ranged from 1 month to 9 years, with a median follow-up of 7 months. SMG flaps were mobilized into the parapharyngeal space (n = 10), parotid bed (n = 4), marginal mandibullectomy defect (n = 3), and inferior to the mandibular body (n = 2). Once mobilized, the glands typically did not retain their usual glandular shape (n = 2), instead becoming distorted (n = 17) with triangular, fusiform, and overall ill-defined morphologies. There was variable CT enhancement, MR imaging enhancement, and MR imaging T2
following resection of a synovial cell sarcoma. MR imaging characteristics of SMG tissue could be discerned at the orthotopic location of the SMG n
hilum, defined as visible ducts and/or a vascular pedicle contiguous with the gland (Fig 4). In all cases, no distinct glandular tissue was discerned at the orthotopic location of the SMG (dashed arrow) in the first image, but decreased in signal intensity in the fat-suppressed image.

信号强度的SMG皮瓣相比于对侧非手术腺体的信号强度，两者信号强度存在差异。大多数被动员的腺体在23例中有异源性表现。最常见的表现是在腺体下颌下间隙，有可见的导管和/or血管芽，与腺体（n = 19）。在所有情况下，没有区别腺体组织可能是由动员腺体在下颌下间隙的原发位置（dashed arrow）在第一张图，但在脂肪抑制图中信号强度降低。

DISCUSSION

Imaging interpretation of the postoperative head and neck can be challenging for the radiologist, in part due to the diverse and complex surgical techniques encountered. To aid in interpretation, previous studies have described in detail the mobilization of glandular tissue, including the thyroid gland during laryngectomy and the SMG for glandular transfer. Therefore, this clinical report aimed to characterize the imaging appearance of the reconstructive SMG flap. In the surgical literature, the SMG flap has been described as an elegant reconstruction to facilitate closure of oropharyngeal defects or restore facial contour following parotidectomy (Fig 2) in instances in which primary closure may result in too much tension of the tissues, while a larger free flap would introduce further complexity of a microvascular operative technique.

The primary pitfall in imaging of SMG flaps in the postsurgical head and neck is that enhancing glandular tissue may be easily mistaken for recurrent tumor (Fig 1). In fact, this mistake was how such a surgical flap was brought to our attention, when a SMG mobilized to the lateral oropharynx was mistakenly interpreted as recurrent tumor. Certainly, in this setting, no adage is more appropriate than that no head and neck imaging interpretation is complete without a priori knowledge of the clinical and surgical history; knowledge of the existence of an SMG flap is of utmost importance for the radiologist. Preoperative imaging is also crucial to differentiate the intermediate enhancement typical of primary tumors from often hyperenhancing glandular tissue. However, recognizing the instances when our interpretations may be bereft of specific, relevant clinical information, we offer these characteristics that may aid the radiologist in recognizing the presence of such a flap (Fig 3).

It may be logical to presume that a gland mobilized for a flap would maintain some semblance of its original imaging characteristics or similarity to the contralateral nonoperative gland. However, enhancement and T2 signal intensity in this series were unpredictable and, therefore, unreliable for gland identification (Fig 4). This issue is due to a variety of opposing factors. Edema and inflammation (eg, postsurgical, immediate postradiation, or localized sialadenitis) increase T2 signal intensity and enhancement. On the contrary, progressive atrophy (eg, long-term postradiation, postinflammatory, or sequelae of chronic ductal obstruction) decreases signal intensity on T2-weighted fat-suppressed and T1-weighted fat-suppressed postcontrast sequences. One notable exception was those glands that were atrophic and replaced by fat preoperatively.
and were invariably fatty in the postoperative period. A fat-replaced gland may introduce a countervailing interpretive pitfall, whereby nodular locally recurrent tumor may be falsely characterized as a normal SMG flap (Fig 5).

To the surgeon, the SMG flap is mobile and pliable, permitting placement in a wide range of useful locations. Thus, the radiologist can anticipate that the gland will largely conform to the surgical defect, depending on the volume of surrounding adipose tissue that is mobilized with the gland. For example, in this series, glands often conformed to the triangular shape of the parapharyngeal space, and those inferior to the mandible were elongated into a fusiform shape (Fig 6). The latter shape is similar to that described in the SMG transfer, yet it is the ipsilateral gland that is mobilized in a SMG flap, and the contralateral gland, for a SMG transfer. While it may seem intuitive, the absence of glandular tissue at the expected orthotopic location of the SMG may be the first clue to the radiologist that the gland has been manipulated, whether mobilized for reconstruction as in the case of the SMG flap or removed as part of the more frequently encountered neck dissection. Otherwise, features of a glandular hilum such as identifiable ducts and/or a vascular pedicle (Fig 7) and heterogeneous hyper-enhancement of a glandular texture (Fig 8) are most useful in identifying a SMG flap and therefore differentiating it from recurrent tumor. As with any reconstructive flap, the margins should be closely evaluated as a site of potential recurrence, with care to differentiate tumor from the gland.

CONCLUSIONS
The SMG flap is a pedicled locoregional reconstruction flap occasionally used following oncologic resection within the head and neck. This feature presents a potential pitfall to the radiologist interpreting posttreatment head and neck examinations because an enhancing SMG flap can be confused with recurrent tumor.
To reduce misdiagnosis, this clinical report raises awareness of this surgical technique and offers a description of the appearance of the SMG flap on CT and MR imaging.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES


ABSTRACT

BACKGROUND AND PURPOSE: Fetal brain MR imaging is clinically used to characterize fetal brain abnormalities. Recently, algorithms have been proposed to reconstruct high-resolution 3D fetal brain volumes from 2D slices. By means of these reconstructions, convolutional neural networks have been developed for automatic image segmentation to avoid labor-intensive manual annotations, usually trained on data of normal fetal brains. Herein, we tested the performance of an algorithm specifically developed for segmentation of abnormal fetal brains.

MATERIALS AND METHODS: This was a single-center retrospective study on MR images of 16 fetuses with severe CNS anomalies (gestation, 21–39 weeks). T2-weighted 2D slices were converted to 3D volumes using a super-resolution reconstruction algorithm. The acquired volumetric data were then processed by a novel convolutional neural network to perform segmentations of white matter and the ventricular system and cerebellum. These were compared with manual segmentation using the Dice coefficient, Hausdorff distance (95th percentile), and volume difference. Using interquartile ranges, we identified outliers of these metrics and further analyzed them in detail.

RESULTS: The mean Dice coefficient was 96.2%, 93.7%, and 94.7% for white matter and the ventricular system and cerebellum, respectively. The Hausdorff distance was 1.1, 2.3, and 1.6 mm, respectively. The volume difference was 1.6, 1.4, and 0.3 mL, respectively. Of the 126 measurements, there were 16 outliers among 5 fetuses, discussed on a case-by-case basis.

CONCLUSIONS: Our novel segmentation algorithm obtained excellent results on MR images of fetuses with severe brain abnormalities. Analysis of the outliers shows the need to include pathologies underrepresented in the current data set. Quality control to prevent occasional errors is still needed.

ABBREVIATIONS: CNN = convolutional neural network; DC = Dice coefficient; IQR = interquartile range

MR imaging of the fetal brain is an important adjunct to ultrasound in the detection and characterization of abnormalities at an early stage of development. High-resolution imaging is essential to accurately diagnose and follow up the evolution of these pathologies. New techniques have allowed the development of isotropic motion-corrected volume reconstructions based on the acquired 2D image stacks, including the so-called super-resolution reconstruction method. These types of volumetric reconstruction methods combine several stacks of 2D slices in different planes to construct a single isotropic volume, removing individual section artifacts and interslice inconsistencies, as well as providing a volume with the same high resolution between slices as within a section. The segmentation of different parts and tissue types of the fetal brain should provide more accurate and more reproducible information regarding the evolution in certain pathologies, such as ventriculomegaly, malformations of cortical development, and tumors.

Performing such segmentation manually requires a high level of expertise and is time-consuming and prone to human error and variability; therefore, accurate automatic segmentation is essential for routine clinical use. Segmentation of the fetal brain is challenging because of the complex and rapidly changing anatomy during fetal life and is further complicated by variable image quality and a variety of artifacts.

In medical image analysis, deep learning methods have recently proved to be very competitive, often outperforming conventional
machine learning and model-based methods, including MR imaging of the adult and normal perinatal brain. Deep neural networks have the major advantage of being able to retrieve specific features for the task at hand directly from the data. The networks learn to extract and interpret features related to the segmentation task without the need to first derive a collection of handcrafted features from the image as input to a classifier or model. The state-of-the-art deep neural networks for segmentation are based on convolutional neural networks (CNNs). The use of automatic segmentation of fetal brain tissues by CNNs has been shown to be effective in normal cases and more recently in cases with spinal dysraphism as well for the ventricles. Developing automated segmentation tools for normal brains may be a good starting point, but in clinical practice, MR imaging is used to assess fetuses with pathology, rather than as a screening tool. Currently, there is a need for robust methods to segment fetal brain structures in the presence of varying severe abnormalities, which are common in the fetal period and can substantially affect the performance of developed techniques.

One of the downsides of using CNNs is that they require large sets of training data. These data also have to be diverse enough for the CNN to be robust to pathologies. Typically, CNNs are trained by using empirical risk minimization to maximize the average segmentation performance. This can cause errors when pathologies are underrepresented in the training data set, as is typically the case with the available abundance of healthy control cases in contrast to the ones with abnormal findings. To address this problem, we specifically developed an algorithm that is more robust to anatomic abnormalities. This algorithm trains a CNN with distributionally robust optimization, which automatically reweighs the training samples with lower performance, encouraging the CNN to perform more consistently on all cases. This method has been shown to be more robust than conventional CNNs trained with empirical risk minimization. This algorithm was validated earlier using 197 fetal brain volumes from 4 different centers, including both normal brains and those with various CNS abnormalities. Using data from multiple centers with MR imaging machines from different vendors with various CNS abnormalities present during testing ensures us that this method of training is especially robust to different data input. This algorithm has since been updated to segment even more brain structures and was validated on a larger data set. The robustness of the algorithm allows the user to input a variety of new cases with abnormal findings with excellent overall generalization results, as is key for the clinical implementation of the algorithm. The acquired segmentations aid in the detection and characterization of fetal pathologies, which could be considered the most important goal of these automatic segmentations.

The algorithm we use automatically segments the cerebellum, ventricular system, and white matter. To ensure the clinical usefulness of this algorithm with distributionally robust optimization, one must evaluate its performance and robustness against the criterion standard, ie, manual segmentation. Therefore, we compared automatic and manual segmentations of different brain structures on a series of super-resolution reconstruction fetal MR imaging volumes of fetal brain malformations.

MATERIALS AND METHODS
The education-support committee of the KU Leuven approved this study.

Data
This was a single-center retrospective study on fetal brain MR imaging, which was performed between October 1, 2016, and February 1, 2020, for CNS anomalies detected on prenatal ultrasound or for an increased risk of CNS anomalies (for diagnosis of included cases, see the Online Supplemental Data). All cases were selected from our data base on fetuses who were assessed because they were at increased risk for/suspected of having CNS abnormalities. Criteria for selection were severe brain malformations of different origins (eg, infectious, destructive, vascular, developmental, and so forth.) In addition, these cases could not have been included in the training data set. If multiple cases of the same pathology were present in the data base, the more severe one was selected. Images were acquired on a clinical 1.5T MR imaging system using a routine clinical protocol, without maternal sedation. This protocol includes T2-weighted single-shot turbo spin-echo sequences of the fetal brain in 3 orthogonal planes (see the Online Supplemental Data for MR imaging parameters), with repetition because of fetal motion when deemed necessary by the attending radiologist (M.A.). 2D slices were reconstructed to isotropic 3D volumes (resolution 0.8 × 0.8 × 0.8 mm) using the super-resolution reconstruction algorithm on a server in the hospital network.

Method
Automatic Segmentation. Isotropic 3D volumes of 16 fetuses were used as input of a CNN, which was trained using distributionally robust optimization for the fully automatic segmentations of the cerebellum, ventricular system, and white matter on both normal and abnormal brains. When we trained the algorithm, it was agreed that the segmentation of the ventricular system would include the lateral, third, and fourth ventricles with the cerebral aqueduct, cavum septum pellucidum, and cavum vergae, when present. The term “white matter” used throughout this article is for ease of use. What eventually becomes white matter consists, during fetal development, of multiple transient layers. Both the automatic and manual segmentations of what is referred to as white matter included these transient layers, more specifically the intermediate zone, cortical subplate, and ventricular zones.

There was no overlap between testing and training data in terms of subjects. The original training data set included 162 patients (124 controls without CNS abnormalities, 28 with spinal dysraphism, and 10 with other CNS abnormalities; see the Online Supplemental Data for more detailed information), with a gestational age range between 21 and 37 weeks.

Manual Segmentation. The reference standard was set by manual segmentation of the selected brain structures, using the automatic segmentations as a starting point. Manual segmentations were performed using the software application ITK-SNAP (Version 3.8.0; www.itksnap.org). These structures were first segmented by a radiology resident (T.D.) and then reviewed and corrected by an experienced fetal radiologist (M.A.).
**RESULTS**

In 2 cases, the super-resolution reconstruction algorithm failed due to severe motion corruption; thus, these images were excluded. The gestational age in the remaining 14 cases was between 21.6 and 39.7 weeks (mean, 27.5 [SD, 4.4] weeks). For each of the 14 cases, the DC, Hausdorff 95%, and volume difference were calculated for the white matter, ventricle system, and cerebellum. Thus, 9 measurements were obtained per case, resulting in 126 measurements. The results of the comparison of automatic-to-manual segmentations are shown in Table 1; total volume and relative volume difference were added as a reference for the volume difference. The median DC for the white matter was 99.5%, which ranged between 64.5% and 99.8%. For the ventricular system, the median DC was 97.4% (range, 75.3%–99.3%). For the cerebellum, the median DC was 96.8% (range, 87.4%–99.1%). The median Hausdorff 95% of the white matter was 0.0 mm (range, 0.0–9.3 mm). For the ventricular system, the median Hausdorff 95% was 1.5 mm (range, 0.0–8.2 mm). For the cerebellum, the median Hausdorff 95% was 1.5 mm (range, 0.8–4.3 mm). The median volume difference for the white matter was 0.4 mL (range, 0.2–14.7 mL); for the ventricular system, it was 0.7 mL (range, 0.1–5.0 mL); and for the cerebellum, it was 0.2 mL (range, 0.0–1.9 mL). Note that the relative volume difference metrics based on all individual data (as in Table 1) is not necessarily the same as the relative comparison of the metrics of volume difference and total volume.

Of the above 126 measurements, there were 16 outliers in 5 fetuses as illustrated in the boxplots of the Figure.

**DISCUSSION**

In this data set of fetuses scanned for CNS abnormalities, we found an overall excellent correlation of automatic and manual segmentations of the white matter, ventricular system, and the cerebellum. This was supported by the high DC, low Hausdorff 95%, and small volume difference. On the basis of our own evaluation of the algorithm, using our data set with abnormal fetal brains, we additionally compared the performance of the CNN with results reported earlier using other methods and data sets (Table 2). DC values of >70% are usually considered consistent with a satisfactory level of agreement between 2 segmentations. This comparison obviously provides only an indication because those studies were performed on other data sets with either healthy fetuses and/or fetuses with different pathologies.

Of the 126 measurements, there were 13% outliers (\(n = 16\)); and artifacts such as the partial volume effect could account for only a minor contributing factor. Conversely, most of these outliers were present in fetuses with very specific anatomic changes. Thus, the outliers are further descriptively discussed on the basis of the underlying condition, hereby identifying when the algorithm makes segmentation errors. This feature emphasizes the limitation of our study, because the number of cases of each pathology is rather small (Online Supplemental Data). As a hypothesis for further research to improve the algorithm, one would need to train the algorithm with additional images with fetal pathologies similar to those in the erroneous cases and at a similar gestational age, to rule out the effect of brain development. This hypothesis is possibly strengthened by the finding that none of the automatic segmentations of the 2 Chiari II cases had outlier

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**Table 1: Evaluation of automatic segmentations for the 14 volumes of abnormal fetal brains**

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<thead>
<tr>
<th></th>
<th>WM</th>
<th>V</th>
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<tbody>
<tr>
<td><strong>DC (%)</strong></td>
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<tr>
<td>Mean</td>
<td>96.4</td>
<td>93.7</td>
<td>94.7</td>
</tr>
<tr>
<td>SD</td>
<td>9.0</td>
<td>7.8</td>
<td>4.4</td>
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<tr>
<td>Median</td>
<td>99.5</td>
<td>97.4</td>
<td>96.8</td>
</tr>
<tr>
<td>IQR</td>
<td>0.8</td>
<td>6.5</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>Hausdorff 95% (mm)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>1.1</td>
<td>2.3</td>
<td>1.6</td>
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<tr>
<td>SD</td>
<td>2.4</td>
<td>2.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Median</td>
<td>0.0</td>
<td>1.5</td>
<td>1.5</td>
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<tr>
<td>IQR</td>
<td>0.8</td>
<td>1.9</td>
<td>0.9</td>
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<tr>
<td><strong>Volume difference (mL)</strong></td>
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<tr>
<td>Mean</td>
<td>1.6</td>
<td>1.4</td>
<td>0.3</td>
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<tr>
<td>SD</td>
<td>3.7</td>
<td>1.6</td>
<td>0.4</td>
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<tr>
<td>Median</td>
<td>0.4</td>
<td>0.7</td>
<td>0.2</td>
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<tr>
<td>IQR</td>
<td>0.5</td>
<td>1.7</td>
<td>0.3</td>
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<tr>
<td><strong>Total volume (mL)</strong></td>
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<tr>
<td>Mean</td>
<td>62.3</td>
<td>25.7</td>
<td>5.3</td>
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<tr>
<td>SD</td>
<td>27.0</td>
<td>52.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Median</td>
<td>57.1</td>
<td>10.1</td>
<td>3.9</td>
</tr>
<tr>
<td>IQR</td>
<td>46.1</td>
<td>7.0</td>
<td>4.6</td>
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<tr>
<td><strong>Relative volume difference (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>7.4</td>
<td>11.4</td>
<td>7.6</td>
</tr>
<tr>
<td>SD</td>
<td>23.2</td>
<td>17.0</td>
<td>6.8</td>
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<tr>
<td>Median</td>
<td>0.7</td>
<td>3.5</td>
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<tr>
<td>IQR</td>
<td>1.0</td>
<td>10.4</td>
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</table>

**Note:** V indicates ventricular system; C, cerebellum.

*Volume difference is calculated by subtracting the manual from automatic segmentations. Total volume (based on manual segmentations) and relative volume differences are added as a reference for volume difference.*

**Evaluation.** To compare the automatic and manual segmentations, we used quantitative methods and a descriptive discussion with reference to the underlying pathology. Quantitative comparison was performed with the Dice coefficient (DC) for volume overlap and the Hausdorff distance at the 95th percentile (Hausdorff 95%) between manual and automatic segmentation, because these were also the 2 metrics that were previously used in the original evaluation of the adopted CNN. We additionally calculated the volume difference between automatic and manual segmentations as an absolute value in Euclidean space. The volume difference was added because of the clinical relevance of volume measurements.

As is common in medical imaging analysis, for a surface-distance parameter, Hausdorff 95% was chosen (rather than at percentile 100). This makes more sense in our study because of the inevitable minor manual segmentation errors, as well as the few stray voxels that are rarely segmented by the CNN, which can even be located outside the skull. These result in a few extremely outliers that do not accurately represent the overall performance. We were particularly interested in measuring the statistical dispersion of the results as a way to evaluate the robustness of the algorithm, as well as to identify outlier values. To this end, we used the SD that is sensitive to outliers and the interquartile range (IQR) that is robust to outliers.

Statistical analysis was performed using Python (https://www.python.org/) and Excel 2016 (Microsoft). To detect outliers, we defined these metric cutoff values as either lower than \(Q1 - (1.5 \times IQR)\) or higher than \(Q3 + (1.5 \times IQR)\), with Q1 and Q3 being the first and third quartiles. These outliers were descriptively discussed in the context of the underlying anomalies on a case-by-case basis.
values, possibly due to the large portion of spinal dysraphism cases in the training data set (28 of the 162 cases).

When we looked at the outlier values of our metrics, we found the most extreme outliers for the white matter and ventricular system in a case of an intracranial hemorrhage, which happened to have a signal intensity similar to that of the developing white matter at the time of imaging. The hemorrhage followed the convexity of the skull bilaterally, deviating the parenchyma medially, thus occupying the space where the white matter is typically found (Online Supplemental Data). This change caused errors in the automatic segmentations, which was to be expected because there were no cases with hemorrhages in the training data set. Because we had a postmortem scan available at the time of manual segmentation, we could verify our manual segmentation and determine that the automatic segmentation algorithm included parts of the hemorrhage in the segmentation of the white matter (see Online Supplemental Data for MR imaging parameters). In the same case, the CNN erroneously included parts of the hemorrhage, extra-axial CSF, as well as porencephalic changes in the segmentation of the ventricular system (Online Supplemental Data). These oversegmentations correspond to the outliers of the DC, Hausdorff 95%, and volume difference for both white matter and the ventricular system.

There was only 1 case with outliers in the segmentation of the cerebellum. This can be explained by the inherent changes due to the pathology present in this case, ie, an aqueductal stenosis. Due to the stenosis, there is a dilation of the supratentorial ventricular system with accompanying mass effect, which, in turn, alters the configuration of the posterior fossa. More precisely, this scenario leads to a redistribution of the pericerebellar CSF and a reduced space between the cerebellum and the tentorium. Presumably, this altered configuration causes undersegmentation of the anterior lobe by the CNN (Online Supplemental Data). The cerebellar folia in the region of the vermis were also undersegmented, due to the partial volume effect brought on by the different distribution of the surrounding CSF. This feature translated into outlier values in Hausdorff 95% and volume difference.

In the same fetus, there were also outliers for the white matter segmentation (both for DC and Hausdorff 95%). The aqueductal stenosis caused dilation of the supratentorial ventricular system and secondary white matter thinning. This result created a thin and irregular segmentation that caused variable DCs, because the DC is inherently highly susceptible to these irregularities (Online Supplemental Data). In addition, this fetus was an outlier due to its advanced gestational age (39.7 weeks), at which time there is advanced gyrification and a decrease in the subcortical tissue throughout the brain, with physiologic remnants in different areas. The combination of both physiologic processes makes the white matter more heterogeneous and probably more difficult for the CNN trained algorithm to segment correctly. The algorithm we used was trained on younger fetuses (21–37 weeks) because these are more commonly scanned; therefore, it had no prior experience with fetuses of that advanced age.

There were also outliers for the ventricular system segmentation in 2 of the 3 cases with (partial) corpus callosum agenesis, in which the CNN makes an oversegmentation of the extraventricular

FIGURE. Results of the automatic segmentations compared with the manual references for the cerebellum, ventricular system, and white matter in our data set of fetuses with severe CNS anomalies. The metrics used are the DC, Hausdorff 95, and volume difference. Outliers are represented by dots in the boxplots. Note that different scales are used for optimal visualization.
CSF in the interhemispheric cistern (Online Supplemental Data). This finding is likely due to the algorithm falsely assuming the presence of a cavum septum pellucidum. This structure is present in healthy fetuses, but absent in corpus callosum agenesis. As mentioned earlier, it was agreed in advance to include the cavum septum pellucidum in the segmentation of the ventricular system (both when training the CNN, as well as for the manual segmentation comparison). This inclusion was because the cavum septum pellucidum is a normal structure in normal fetal brains, though we acknowledge it is not part of the ventricular system. Furthermore, in the training data set, we included several cases with spinal dysraphism in which the cavum septum pellucidum can be absent or incomplete.24,25 In corpus callosum agenesis, the lateral ventricles are generally more widely spaced and the third ventricle is dilated and may communicate with the interhemispheric fissure. Therefore, we hypothesize that the algorithm recognizes the fluid-filled space or associated cyst between the hemispheres as the cavum septum pellucidum.

In one of these 2 cases, a borderline outlier was also seen in the white matter volume difference, presumably because of the partial volume effect in the narrow parts of the lateral ventricles, in turn causing lower-signal-intensity voxels of the CSF to be wrongfully included (Online Supplemental Data).

Finally, there was an outlier in the DC of the white matter in a case with idiopathic dilation of the lateral ventricles. We attribute this to the previously mentioned factors of thin and irregular white matter due to ventriculomegaly (Online Supplemental Data). We have focused on the outliers because they are the most interesting for further development of segmentation algorithms. For completion, we have also added an example of a case in which the algorithm performs well; thus, there is a good correlation of the automatic and the manual segmentations (Online Supplemental Data).

Note that the commissures were not added to the white matter segmentation, even though we acknowledge that commissural fibers are white matter. This decision was due to additional brain structures being added in later versions of the algorithm, which include commissural fibers such as the corpus callosum.

Another potential limitation is that the manual segmentation was performed using the automatic segmentation as a starting point. This step was to simultaneously identify potential errors in the automatic segmentation, being important to the engineers involved in the development and further optimization of the algorithm. To minimize the potential effect on the statistical results, we reviewed the manual segmentations and an experienced fetal radiologist (M.A.) corrected them after the initial manual segmentation by a radiology resident (T.D.). As a final limitation, we acknowledge the small number of cases of each pathology, which has been mentioned before in this section.

CONCLUSIONS

We demonstrated an overall excellent correlation between the automatic segmentation by the CNN and the ground truth manual segmentations in a new clinical data set, consisting exclusively of cases with a variety of severe brain abnormalities. Additionally, our results suggest the need to include enough cases with a diverse spectrum of pathologies and a broad age range when training these algorithms to prevent errors. The remaining errors emphasize the need to perform a manual check and look for occasional faults of the algorithm due to severe or rare abnormalities or induced by artifacts. Nevertheless, the vast time savings would suggest that this algorithm is very useful for managing clinical data sets with a variety of pathologies.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES


Table 2: Automatic segmentation performance on our testing data set (trained using distributionally robust optimization) compared with other methods trained and evaluated with different data sets

<table>
<thead>
<tr>
<th>Our Data Set</th>
<th>Habas et al26</th>
<th>Serag et al27</th>
<th>Khalili et al11</th>
<th>Gholipour et al4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal data set</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Normal</td>
<td>Not specified</td>
</tr>
<tr>
<td>WM</td>
<td>96.2 (9.0)</td>
<td>90.0 (2.0)</td>
<td>90.0 (6.0)</td>
<td>91.9</td>
</tr>
<tr>
<td>V</td>
<td>93.7 (7.8)</td>
<td>90.0 (2.0)</td>
<td>92.0 (4.0)</td>
<td>87.4</td>
</tr>
<tr>
<td>C</td>
<td>94.7 (4.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: — indicates ventricular system; C, cerebellum.

*We report the mean DC [%]. SD is noted in parentheses (when available). Performance of previous methods is taken from the literature. Hence, this comparison can be used as an indication only. Whether the test data set contains normal and/or abnormal fetal brains is specified in the row “Fetal data set.”
Temporal Characteristics of CSF-Venous Fistulas on Digital Subtraction Myelography


ABSTRACT

BACKGROUND AND PURPOSE: CSF-venous fistula can be diagnosed with multiple myelographic techniques; however, no prior work has characterized the time to contrast opacification and the duration of visualization. The purpose of our study was to evaluate the temporal characteristics of CSF-venous fistula on digital subtraction myelography.

MATERIALS AND METHODS: We reviewed the digital subtraction myelography images of 26 patients with CSF-venous fistulas. We evaluated how long the CSF-venous fistula took to opacify after contrast reached the spinal level of interest and how long it remained opacified. Patient demographics, CSF-venous fistula treatment, brain MR imaging findings, CSF-venous fistula spinal level, and CSF-venous fistula laterality were recorded.

RESULTS: Eight of the 26 CSF-venous fistulas were seen on both the upper- and lower-FOV digital subtraction myelography, for a total of 34 CSF-venous fistula views evaluated on digital subtraction myelography. The mean time to appearance was 9.1 seconds (range, 0–30 seconds). Twenty-two (84.6%) of the CSF-venous fistulas were on the right. The highest fistula level was C7, while the lowest was T13 (13 rib-bearing vertebral bodies). The most common CSF-venous fistula levels were T6 (4 patients) followed by T8, T10, and T11 (3 patients each). The mean age was 58.3 years (range, 31.7–87.6 years). Sixteen patients were women (61.5%).

CONCLUSIONS: This is the first study to report the temporal characteristics of CSF-venous fistulas using digital subtraction myelography. We found that on average, the CSF-venous fistula appeared 9.1 seconds (range, 0–30 seconds) after intrathecal contrast reached the spinal level.

ABBREVIATIONS: CTM = CT myelography; CVF = CSF-venous fistula; DSM = digital subtraction myelography; SIH = spontaneous intracranial hypotension
spine. When the CVF was seen in both the upper and lower DSM images on the same patient, the temporal characteristics were averaged. In cases in which the CVF was no longer visualized before the last image, we also noted whether intrathecal contrast remained at that spinal level.

Additional patient information such as sex, age, and treatment were recorded. Pre-DSM brain MR imaging was evaluated by a neuroradiologist (A.M.) for signs of SIH using a previously described quantitative scale (Bern score).6

**DSM Technique**

All DSMs were performed with the patient under moderate sedation in the lateral decubitus position on a tilttable with or without a wedge to elevate the patient’s hips to achieve approximately 4°–8° of spinal tilt.7 Imaging was performed at a rate of 1 frame/second. The thecal sac was accessed at L2–L3 or below with a 20- or 22-ga needle, with the intrathecal needle position confirmed by 0.5 mL of iohexol (Omnipaque 300; GE Healthcare). Approximately 5–10 mL of normal saline was slowly infused into the thecal sac for pressurization followed by a hand injection of 6 mL of Omnipaque, while imaging from the cervicothoracic junction to the lower thoracic spine; the caudal FOV depended on the patient’s body habitus. We used 5–10 mL of normal saline to flush the line. Then, a second bolus of 5 mL of contrast was injected while imaging from the needle access site and extending cranially, normally extending to the mid-thoracic spine. The connecting tube and needle were cleared with sterile saline, but we did not routinely pressurize the thecal sac with saline after this contrast injection. The duration of image acquisition was determined by the individual proceduralist. This variability was 1 factor that led to our desire to study CVF temporal characteristics.

**RESULTS**

**Patient Demographics and Brain MR Imaging Findings**

Twenty-six patients with CVF on DSM were included in this study. The mean age was 58.3 years (range, 31.7–87.6 years). Sixteen patients were women (61.5%). The mean Bern score was 4.2 (SD, 2.6) (range, 0–8). The occurrence of SIH findings was as follows: suprasellar cistern effacement of ≤4 mm (61.5%), pachymeningeal enhancement (57.7%), venous sinus engorgement (15.4%), subdural fluid collection (7.7%), preptone cistern effacement of ≤5 mm (80.8%), and mamillopontine distance of ≤6.5 mm (80.8%). None of the patients had been treated with transvenous catheter embolization, epidural blood patch, fibrin glue injection, or surgical ligation before DSM. All patients underwent transvenous catheter embolization with Onyx (Medtronic) for treatment after DSM.

**CVF Level and Laterality**

The highest fistula level was C7, while the lowest was T13 (13 rib-bearing vertebral bodies). The most common CVF levels were T6 (4 patients) followed by T8, T10, and T11 (3 patients each). Twenty-two (84.6%) CVFs were on the right side. Patient-specific details are listed in the Table.

**CVF Temporal Characteristics**

Of the 26 patients, 8 had CVFs that were seen on the upper and lower runs. The mean time from contrast reaching the spinal level to the time of CVF appearance was 9.1 seconds (range, 0–30 seconds). The mean duration of CVF opacification was 48.1 seconds (range, 24–73 seconds). An imaging example of the CVF temporal characteristics on DSM is shown in the Figure. Of the 34 CVFs, 18 CVFs remained opacified on the last DSM image acquired, so we could not assess further duration of contrast opacification beyond the final acquired image. Sixteen CVFs disappeared before the last DSM image, with a mean CVF duration of 49.8 seconds (range, 24–68 seconds). Of the 16 CVFs that disappeared before the last image, 14 (87.5%) had intrathecal contrast at the CVF level (6 of which were faint) and 2 (12.5%) no longer had intrathecal contrast at the CVF level.

**CVF Temporal Characteristics by Location**

Thirteen CVFs were in the cervical or upper thoracic spine (C7–T6), with a mean time to appearance of 7.0 seconds (range, 1–15.5 seconds), a mean duration of contrast opacification of 49.3 seconds (range, 27–72 seconds), and a mean combined time of 56.3 seconds. The 13 CVFs in the lower thoracic spine (T7–T13) had a similar mean combined time of 58.0 seconds, but a slightly longer mean time to appearance (11.2 seconds) and a shorter mean duration (46.8 seconds).

**DSM Upper-versus-Lower Runs**

The spinal level of the CVF was within the FOV in both the upper and lower runs in 13 patients. All were seen on the upper run, compared with only 8 (61.5%) on the lower run. All cases

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### Individual CVF information that includes the laterality, spinal level, and temporal characteristics

<table>
<thead>
<tr>
<th>Side</th>
<th>Level</th>
<th>Upper: Time to Appear/Duration (sec)</th>
<th>Lower: Time to Appear/Duration (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>C7</td>
<td>12/37+</td>
<td>—</td>
</tr>
<tr>
<td>R</td>
<td>T1</td>
<td>10/46+</td>
<td>—</td>
</tr>
<tr>
<td>T2</td>
<td>3/27+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>T2</td>
<td>12/28+</td>
<td>—</td>
</tr>
<tr>
<td>R</td>
<td>T3</td>
<td>3/59+</td>
<td>—</td>
</tr>
<tr>
<td>R</td>
<td>T4</td>
<td>1/54</td>
<td>—</td>
</tr>
<tr>
<td>R</td>
<td>T4</td>
<td>6/72+</td>
<td>N</td>
</tr>
<tr>
<td>R</td>
<td>T5</td>
<td>2/51+</td>
<td>N</td>
</tr>
<tr>
<td>L</td>
<td>T5</td>
<td>5/52</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>T6</td>
<td>5/41</td>
<td>—</td>
</tr>
<tr>
<td>L</td>
<td>T6</td>
<td>7/67+</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>T6</td>
<td>11/68</td>
<td>7/67</td>
</tr>
<tr>
<td>L</td>
<td>T7</td>
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<tr>
<td>R</td>
<td>T7</td>
<td>16/24</td>
<td>10/38</td>
</tr>
<tr>
<td>R</td>
<td>T8</td>
<td>4/51+</td>
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</tr>
<tr>
<td>R</td>
<td>T13</td>
<td>6/42+</td>
<td></td>
</tr>
</tbody>
</table>

**Note:**—The en dash indicates not in the FOV; N, not seen but in the FOV; +, the CVF is opacified on the last image; R, right; L, left.
followed our standard technique, with the upper run acquired before the lower run.

**DISCUSSION**

In the current study, we evaluated the temporal characteristics of CVF on DSM. We found that CVFs take 9.1 seconds to appear once contrast reaches the spinal level of the CVF and remain visible for an additional 48.1 seconds. Because CVFs are challenging to diagnose, multiple modalities (DSM, CTM, MR myelography) and image-acquisition timing (dynamic-versus-nondynamic) have been used. The variety of myelographic techniques is due, in part, to resource availability as well as lack of understanding of how and when CVFs opacify with contrast. This is the first study to evaluate CVF temporal characteristics and could help to improve future myelographic techniques in the evaluation of CVF.

CVFs were first described with DSM.8 Since that discovery, multiple modalities have been used for CVF diagnosis.7,9,10 DSM has the advantage of higher temporal resolution because our technique acquires images at a rate of 1 frame per second. One challenge with DSM lies in the uncertainty of knowing how long to image. The dilemma of when to image and for how long could also apply to CTM. Prior work describing ultrafast dynamic CTM reported approximately 15 seconds per acquisition of the cervical and thoracic spine.11 The acquisition time would be longer when including the lumbar spine.

Depending on the table tilt, spine curvature, and CSF dynamics, our practice observes intrathecal contrast flowing at various rates during DSM. Therefore, we measured the time of CVF appearance from when the contrast reached the spinal level. We found that on average, CVFs opacify with contrast 9.1 seconds after intrathecal contrast reaches the CVF level. Twelve of 33 (36.4%) CVFs opacified within the first 5 seconds, while 5 (18.2%) took at least 15 seconds to appear. On average, the CVF remained opacified for 48.1 seconds. Only 3 (9.1%) CVFs disappeared before 30 seconds, while 18 (52.9%) remained opacified on the final image. If the spine were imaged 30 seconds after the contrast reached a particular spinal level, all cases of CVF from our cohort would be seen on at least 1 frame.

Prior work has suggested that respiratory techniques during myelography could help opacify the CVF. Amrhein et al12 described increased conspicuity of the CVF at end-inspiration. Other work has shown that the CSF-to-venous pressure gradient can be increased with resisted inspiration.13 It is unknown how resisted inspiration would affect the temporal characteristics of CVF, but it could conceivably decrease the time to appearance and duration. The duration of CVF opacification should depend, in part, on the venous outflow, with most CVFs draining into the azygos system and, in turn, into the superior vena cava (SVC). Prior work has shown that the SVC-azygos junction can have efferent flow depending on the cardiac cycle,14 which could further delay emptying of the azygos system. The effect of general anesthesia and positive pressure ventilation are unknown, but increased intrathoracic pressure could pressurize the azygos system and contribute to delayed opacification and emptying of the CVF. While general anesthesia would optimize motion control, we did not find that motion obscured CVF visualization in our cases.

![FIGURE](https://example.com/figure.png)
Thirteen of our patients had CVFs at a spinal level that was within the FOV on both the upper and lower runs of the DSM. The CVF was visualized on the upper run in all cases. Most interesting, only 61.5% of CVFs were also seen on the lower run, despite being within the FOV. In each of these cases, the upper run was acquired first, and the lower run, second. This result could be attributed to the use of a postcontrast saline chaser for the upper run but not the lower run. Work by Caton et al\(^\text{15}\) suggests that a CVF may need a certain pressure to open; likewise, there may be a subsequent pressure drop. With our technique, the contrast from the lower run and the lack of a saline chaser may not provide the necessary pressure to open the CVF seen on the upper run. The ideal saline chaser size and rate of infusion are not known, but theoretically, a more robust chaser could make the CVF appear sooner. Further study comparing the DSM yield with and without positive pressurization of the thecal sac could better elucidate these observations.

Our study has limitations. Our sample size is small, just 26 patients, yet this represents one of the largest studies on CVF using DSM. A larger sample size may help to categorize the temporal characteristics by spinal level. Second, the CVF was opacified on the last image in more than one-half of our patients; therefore, we do not know the true duration of opacification. This limitation falsely decreases the calculated duration of opacification. Also, we imaged patients for only a short duration after the injection of contrast. Prior work has used a delayed image acquisition with conventional nondynamic CT\(^\text{16}\) and MR myelography\(^\text{17,18}\) to evaluate CVFs. Therefore, it would be difficult to apply our findings to those cases of delayed imaging. Additionally, dynamic myelography technique can differ at each institution (modality, saline chaser, contrast amount, breathing instructions) and, therefore, limits the generalization of these results. Finally, we were unable to detail the time between the injection of contrast and the time of first image acquisition. While our typical procedure has a 5- to 7-second delay, this is variable and it cannot be measured retrospectively.

**CONCLUSIONS**

This is the first study to report on the temporal characteristics of CVF using DSM. We found that on average, the CVF appeared 9.1 seconds after the intrathecal contrast reached the CVF spinal level.

Disclosures provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

**REFERENCES**


